```
FILE 'HOME' ENTERED AT 15:11:53 ON 30 JUN 2009

=> file medline scisearch embase
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.22       0.22

FILE 'MEDLINE' ENTERED AT 15:12:31 ON 30 JUN 2009

FILE 'SCISEARCH' ENTERED AT 15:12:31 ON 30 JUN 2009
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FILE 'EMBASE' ENTERED AT 15:12:31 ON 30 JUN 2009
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=> s standard proteasome
L1          55 STANDARD PROTEASOME

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2           35 DUP REM L1 (20 DUPLICATES REMOVED)

=> s tunor antigen
L3           1 TUNOR ANTIGEN

=> s tumor antigen
L4       24972 TUMOR ANTIGEN

=> s l4 and l2
L5           1 L4 AND L2

=> d ibib abs

L5   ANSWER 1 OF 1  SCISEARCH  COPYRIGHT (c) 2009 The Thomson Corporation  on
     STN
ACCESSION NUMBER:    2007:46232  SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 121NT
TITLE:               Identification of a highly immunogenic HLA-A]01-binding T
                     cell epitope of WT1
AUTHOR:              Scheibenbogen, Carmen (Reprint)
CORPORATE SOURCE:    Med Klin 3, Charite, Campus Benjamin Franklin,
                     Hindenburgdamm 30, D-12200 Berlin, Germany (Reprint)
AUTHOR:              Asemissen, Anne Marie; Keilholz, Ulrich; Tenzer, Stefan;
                     Mueller, Margret; Walter, Steffen; Stevanovic, Stefan;
                     Schild, Hansjoerg; Letsch, Anne; Thiel, Eckhard;
                     Rammensee, Hans-Georg
CORPORATE SOURCE:    Med Klin 3, Charite, D-12200 Berlin, Germany; Univ Mainz,
                     Inst Immunol, D-6500 Mainz, Germany; Univ Tubingen, Inst
                     Zellbiol, Immunol Abt, Tubingen, Germany; Inst Med
                     Immunol, Charite, Berlin, Germany
                     E-mail: carmen.scheibenbogen@charite.de
COUNTRY OF AUTHOR:   Germany
SOURCE:              CLINICAL CANCER RESEARCH, (15 DEC 2006) Vol. 12, No. 24,
                     pp. 7476-7482.
                     ISSN: 1078-0432.
PUBLISHER:           AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR,
                     PHILADELPHIA, PA 19106-4404 USA.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     49
ENTRY DATE:          Entered STN: 18 Jan 2007
```

Last Updated on STN: 18 Jan 2007
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose: The transcription factor Wilms tumor protein 1 (WT1) belongs to a new generation of tumor antigens, as it is essential for tumor cell proliferation and is highly expressed in various hematologic and solid malignancies. The aim of this study was to apply a modified reverse immunology strategy to identify immunogenic epitopes of WT1 which could be useful for immunotherapy.

Experimental Design: Potential HLA-A*01 epitopes predicted by a MHC binding algorithm were screened for recognition by peripheral blood mononuclear cells (PBMC) from patients with spontaneous T cell responses using intracellular cytokine cytometry. Epitope processing was shown by proteasomal cleavage. Epitope-specific T cells were generated from CD4+CD25+ regulatory T cell - depleted PBMC.

Results: One of five predicted HLA-A*01-binding candidate epitopes showed high immunogenicity as 5 of 14 patients with hematologic malignancies had WT1.317-327-reactiveTcells ranging from 0.4% to 1.5% of CD3+CD8+ T cells. Proteasomal degradation assays indicated the cleavage of WT1.317-327. The depletion of regulatory T cells from PBMCs enabled the rapid expansion of WT1.317-327-specific CTL, whereas no CTL could be generated from unfractionated PBMC. WT1.317-327-specific CTL efficiently lysed an autologous WT1-expressing tumor cell line but not HLA-A*01 - negative WT1-expressing tumor cells. Immunogenicity of the epitope across histologies was verified by the demonstration of spontaneous ex vivo WT1.317-327-specific T cell responses in two of six patients with HLA-A*01 - positive melanoma or lung cancer.

Conclusion: In this study, a modified reverse immunology strategy was employed to identify a first immunogenic HLA-A*01 - restricted T cell epitope of the tumor antigen WT1, which is of considerable interest for use in vaccination trials.

```
=> s melanA and 27()35
AND IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s melanA (a) 27()35
L6            4 MELANA (A) 27(W) 35

=> s melanA (s) 27()35
L7            4 MELANA (S) 27(W) 35

=> s melanA  27()35
L8            4 MELANA 27(W) 35

=> d ibib abs 1-4

L8   ANSWER 1 OF 4     MEDLINE on STN
ACCESSION NUMBER:    2003008601     MEDLINE <<LOGINID::20090630>>
DOCUMENT NUMBER:     PubMed ID: 12491520
TITLE:               Granulocyte-macrophage-colony-stimulating factor added to a
                     multipeptide vaccine for resected Stage II melanoma.
AUTHOR:              Weber Jeffrey; Sondak Vernon K; Scotland Ronaldo; Phillip
                     Ramila; Wang Flora; Rubio Valerie; Stuge Tor B; Groshen
                     Susan G; Gee Conway; Jeffery Georgia G; Sian Shirley; Lee
                     Peter P
CORPORATE SOURCE:    Department of Medicine, Division of Medical Oncology,
                     Keck/University of Southern California School of Medicine,
                     Los Angeles, CA, USA.. jweber@hsc.usc.edu
```

CONTRACT NUMBER: 5P30 CA 14089 (United States NCI NIH HHS)
R01 CA 090809 (United States NCI NIH HHS)
SOURCE: Cancer, (2003 Jan 1) Vol. 97, No. 1, pp. 186-200.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 8 Jan 2003
Last Updated on STN: 25 Jan 2003
Entered Medline: 24 Jan 2003

AB BACKGROUND: Forty-eight patients with resected Stages IIA and IIB melanoma were immunized with two tumor antigen epitope peptides derived from gp100(209-217) (210M) (IMDQVPSFV) and tyrosinase(368-376) (370D) (YMDGTMSQV) emulsified with incomplete Freund's adjuvant (IFA). Patients were assigned randomly to receive either peptides/IFA alone or with 250 microm of granulocyte-macrophage-colony-stimulating factor (GM-CSF) subcutaneously daily for 5 days to evaluate the toxicities and immune responses in either arm. Time to recurrence and survival were secondary end points. METHODS: Immunizations were administered every 2 weeks x 4, then every 4 weeks x 3, and once 8 weeks later. A leukapheresis to obtain peripheral blood mononuclear cells for immune analyses and skin testing with peptides and recall reagents was performed before and after eight vaccinations. RESULTS: Local pain and granuloma formation, fever, and lethargy of Grade 1 or 2 were observed. Transient vaccine-related Grade III and no Grade IV toxicity was observed. Seventeen of the 40 patients for whom posttreatment skin tests were performed developed a positive skin test response to the gp100 peptide, but only 1 of the 40 patients developed a positive skin test response to tyrosinase. Immune responses were measured by release of interferon-gamma (IFN-gamma) in an enzyme-linked immunosorbent assay (ELISA) by effector cells in the presence of peptide-pulsed antigen-presenting cells, by cytokine release of IFN-gamma, GM-CSF, and tumor necrosis factor-alpha in a Luminex assay, or by an antigen-specific tetramer flow cytometry assay. Thirty-four of the 39 patients for whom the ELISA data were performed demonstrated an immune response after vaccination, as did 37 of 42 patients by tetramer assay. Enzyme-linked immunosorbent assay, Luminex, and tetramer responses in the GM-CSF/peptide/IFA group were higher than in the peptide/IFA group. Epitope spreading to the MART-1/MelanA 27-35
and 26-35 (27L) epitopes was detected by tetramer assay in 10 patients. Seven of 48 patients experienced disease recurrence with a median of 24 months of follow-up and 2 patients in this intermediate to high risk group have died. CONCLUSION: These data suggest a significant number of patients with resected melanoma mount an antigen-specific immune response against a peptide vaccine. There is a trend for GM-CSF to modestly increase the immune response and support further development of GM-CSF as a vaccine adjuvant.

L8 ANSWER 2 OF 4 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:91626 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 634BE
TITLE: Granulocyte-macrophage-colony-stimulating factor added to a multipeptide vaccine for resected stage II melanoma

AUTHOR: Weber J (Reprint)
CORPORATE SOURCE: Univ So Calif, Kenneth Norris Jr Comprehens Canc Ctr, Room 6428, 1441 Eastlake Ave, Los Angeles, CA 90089 USA (Reprint)
AUTHOR: Sondak V K; Scotland R; Phillip R; Wang F; Rubio V; Stuge T B; Groshen S G; Gee C; Jeffery G G; Sian S; Lee P P
CORPORATE SOURCE: Univ So Calif, Keck Sch Med, Dept Med, Div Med Oncol, Los Angeles, CA USA; Univ Michigan, Sch Med, Dept Surg, Ann Arbor, MI USA; Upstate Grp Inc, Charlottesville, VA USA; Stanford Univ, Sch Med, Dept Med, Div Hematol, Stanford, CA 94305 USA; Keck Univ So Calif, Sch Med, Dept Prevent Med, Los Angeles, CA USA
COUNTRY OF AUTHOR: USA
SOURCE: CANCER, (1 JAN 2003) Vol. 97, No. 1, pp. 186-200. ISSN: 0008-543X.
PUBLISHER: JOHN WILEY & SONS INC, 111 RIVER ST, HOBOKEN, NJ 07030 USA
.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 72
ENTRY DATE: Entered STN: 7 Feb 2003
Last Updated on STN: 7 Feb 2003
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB BACKGROUND. Forty-eight patients with resected Stages IIA and IIB melanoma were immunized with two tumor antigen epitope peptides derived from gp100(209-217) (210M) (IMDQVPSFV) and tyrosinase(368-376) (370D) (YMDGTMSQV) emulsified with incomplete Freund's adjuvant (IFA). Patients were assigned randomly to receive either peptides/IFA alone or with 250 mum of granulocyte-macrophage-colony-stimulating factor (GM-CSF). subcutaneously daily for 5 days to evaluate the toxicities and immune responses in either arm. Time to recurrence and survival were secondary end points.

METHODS. immunizations were administered every 2 weeks x 4, then every 4 weeks x 3, and once 8 weeks later. A leukapheresis to obtain peripheral blood mononuclear cells for immune analyses and skin testing with peptides and recall reagents was performed before and after eight vaccinations.

RESULTS. Local pain and granuloma formation, fever, and lethargy of Grade 1 or 2 were observed. Transient vaccine-related Grade III and no Grade IV toxicity was observed. Seventeen of the 40 patients for whom posttreatment skin tests were performed developed a positive skin test response to the gp100 peptide, but only 1 of the 40 patients developed a positive skin test response to tyrosinase. Immune responses were measured by release of interferon-gamma (IFN-gamma) in an enzyme-linked immunosorbent assay (ELISA) by effector cells in the presence of peptide-pulsed antigen-presenting cells, by cytokine release of IFN-gamma, GM-CSF, and tumor necrosis factor-alpha in a Luminex assay, or by an antigen-specific tetramer flow cytometry assay. Thirty-four of the 39 patients for whom the ELISA data were performed demonstrated an immune response after vaccination, as did 37 of 42 patients by tetramer assay. Enzyme-linked immunosorbent assay, Luminex, and tetramer responses in the GM-CSF/peptide/IFA group were higher than in the peptide/IFA group. Epitope spreading to the MART-1/MelanA 27-35
and 26-35 (27L) epitopes was detected by tetramer assay in 10 patients. Seven of 48 patients experienced disease recurrence with a median of 24 months of follow-up and 2 patients in this intermediate to high risk group have died.

CONCLUSION. These data suggest a significant number of patients with resected melanoma mount an antigen-specific immune response against a peptide vaccine. There is a trend for GM-CSF to modestly increase the immune response and support further development of GM-CSF as a vaccine

adjuvant.

L8 ANSWER 3 OF 4 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:198231 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 175QB
TITLE: Assessment of immunogenicity of human melan-A peptide analogues in HLA-A]0201/K-b transgenic mice
AUTHOR: Miconnet I (Reprint)
CORPORATE SOURCE: Univ Lausanne, Ludwig Inst Canc Res, Lausanne Branch, Chemin Boveresses 155, CH-1066 Epalinges, Switzerland (Reprint)
AUTHOR: Men Y; Valmori D; Rimoldi D; Cerottini J C; Romero P
CORPORATE SOURCE: Univ Lausanne, Ludwig Inst Canc Res, Lausanne Branch, CH-1066 Epalinges, Switzerland; CHU Vaudois, Ludwig Inst Canc Res, Lausanne Branch, Div Clin Oncoimmunol, CH-1011 Lausanne, Switzerland
COUNTRY OF AUTHOR: Switzerland
SOURCE: JOURNAL OF IMMUNOLOGY, (15 MAR 1999) Vol. 162, No. 6, pp. 3566-3573.
ISSN: 0022-1767.
PUBLISHER: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 56
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Previous studies have shown that substitution of single amino acid residues in human Melan-A immunodominant peptides MelanA(27-35) and Melan-A(26-35) greatly improved their binding and the stability of peptide/HLA-A*0201 complexes. In particular, one Melan-A peptide analogue was more efficient in the generation of Melan-A peptide-specific and melanoma-reactive CTL than its parental peptide in vitro from human PDL. In this study, we analyzed the in vivo immunogenicity of Melan-A natural peptides and their analogues in HLA-A*0201/K-b transgenic mice. We found that two human Melan-A natural peptides, Melan-A(26-35) and Melan-A(27-35), were relatively weak immunogens, whereas several Melan-A peptide analogues were potent immunogens for in vivo CTL priming. In addition, induced Melan-A peptide-specific mouse CTL cross-recognized natural Melan-A peptides and their analogues. More interestingly, these mouse CTL were also able to lyse human melanoma cell lines in vitro in a HLA-A*0201-restricted, Melan-A-specific manner. Our results indicate that the HLA-A*0201/K-b transgenic mouse is a useful animal model to perform preclinical testing of potential cancer vaccines, and that Melan-A peptide analogues are attractive candidates for melanoma immunotherapy.

L8 ANSWER 4 OF 4 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003012603 EMBASE <<LOGINID::20090630>>
TITLE: Granulocyte-macrophage-colony-stimulating factor added to a multipeptide vaccine for resected Stage II melanoma.
AUTHOR: Weber, Jeffrey, Dr. (correspondence); Scotland, Ronaldo; Wang, Flora; Gee, Conway; Jeffery, Georgia G.; Sian, Shirley
CORPORATE SOURCE: Department of Medicine, Division of Medical Oncology, Keck/Univ. of S. CA Sch. of Med., Los Angeles, CA, United States. jweber@hsc.usc.edu
AUTHOR: Sondak, Vernon K.

CORPORATE SOURCE: Department of Surgery, Univ. of Michigan School of Medicine, Ann Arbor, MI, United States.
AUTHOR: Phillip, Ramila
CORPORATE SOURCE: Upstate Group, Inc., Charlottesville, VA, United States.
AUTHOR: Rubio, Valerie; Stuge, Tor B.; Lee, Peter P.
CORPORATE SOURCE: Department of Medicine, Division of Hematology, Stanford Univ. School of Medicine, Stanford, CA, United States.
AUTHOR: Groshen, Susan G.
CORPORATE SOURCE: Department of Preventive Medicine, Keck/Univ. of S. CA Sch. of Med., Los Angeles, CA, United States.
AUTHOR: Weber, Jeffrey, Dr. (correspondence)
CORPORATE SOURCE: USC/Norris Compreh. Cancer Center, 1441 Eastlake Avenue, Los Angeles, CA 90089, United States. jweber@hsc.usc.edu
SOURCE: Cancer, (1 Jan 2003) Vol. 97, No. 1, pp. 186-200.
Refs: 72
ISSN: 0008-543X CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jan 2003
Last Updated on STN: 16 Jan 2003

AB BACKGROUND. Forty-eight patients with resected Stages IIA and IIB melanoma were immunized with two tumor antigen epitope peptides derived from gp100(209-217) (210M) (IMDQVPSFV) and tyrosinase(368-376) (370D) (YMDGTMSQV) emulsified with incomplete Freund's adjuvant (IFA). Patients were assigned randomly to receive either peptides/IFA alone or with 250 μm of granulocyte-macrophage-colony-stimulating factor (GM-CSF) subcutaneously daily for 5 days to evaluate the toxicities and immune responses in either arm. Time to recurrence and survival were secondary end points. METHODS. Immunizations were administered every 2weeks x 4, then every 4 weeks x 3, and once 8 weeks later. A leukapheresis to obtain peripheral blood mononuclear cells for immune analyses and skin testing with peptides and recall reagents was performed before and after eight vaccinations. RESULTS. Local pain and granuloma formation, fever, and lethargy of Grade 1 or 2 were observed. Transient vaccine-related Grade III and no Grade IV toxicity was observed. Seventeen of the 40 patients for whom posttreatment skin tests were performed developed a positive skin test response to the gp100 peptide, but only 1 of the 40 patients developed a positive skin test response to tyrosinase. Immune responses were measured by release of interferon-gamma (IFN-γ) in an enzyme-linked immunosorbent assay (ELISA) by effector cells in the presence of peptide-pulsed antigen-presenting cells, by cytokine release of IFN-γ, GM-CSF, and tumor necrosis factor-alpha in a Luminex assay, or by an antigen- specific tetramer flow cytometry assay. Thirty-four of the 39 patients for whom the ELISA data were performed demonstrated an immune response after vaccination, as did 37 of 42 patients by tetramer assay. Enzyme-linked immunosorbent assay, Luminex, and tetramer responses in the GM-CSF/peptide/IFA group were higher than in the peptide/IFA group. Epitope spreading to the MART-1/MelanA 27-35 and 26-35 (27L) epitopes was detected by tetramer assay in 10 patients. Seven of 48 patients experienced disease recurrence with a median of 24 months of follow-up and 2 patients in this intermediate to high risk group have died. CONCLUSION. These data suggest a significant number of patients with resected melanoma mount an antigen-specific immune response against a peptide vaccine. There is a

trend for GM-CSF to modestly increase the immune response and support further development of GM-CSF as a vaccine adjuvant. .COPYRGT. 2003 American Cancer Society.

=> s housekeeping proteasome
L9 7 HOUSEKEEPING PROTEASOME

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10 3 DUP REM L9 (4 DUPLICATES REMOVED)

=> d ibib abs 1-4

L10 ANSWER 1 OF 3 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2009004843 EMBASE <<LOGINID::20090630>>
TITLE: Multiple forms of proteasomes and their role in tumor fate.
AUTHOR: Sharova, Natalie (correspondence); Zakharova, Liudmila
CORPORATE SOURCE: N.K. Koltsov Institute of Developmental Biology, Russian Academy of Sciences, Vavilova St. 26, Moscow 119334, Russian Federation. npsharova@bk.ru
SOURCE: Recent Patents on Endocrine, Metabolic and Immune Drug Discovery, (2008) Vol. 2, No. 3, pp. 152-161. Refs: 97
ISSN: 1872-2148
PUBLISHER: Bentham Science Publishers B.V., P.O. Box 294, Bussum, 1400 AG, Netherlands.
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jan 2009
Last Updated on STN: 30 Jan 2009

AB Mammalian and human cells contain multiple forms of proteasomes different in their structure and functions. 26S-proteasome pool regulates most cellular processes through ATP- and ubiquitin-dependent hydrolysis of proteins participating in these processes. This function is possible due to 19S-subparticle capable to recognize ubiquitinated proteins, unfold and direct them into the proteolytic chamber. 20S-proteasome pool is capable to degrade some damaged and foreign proteins in an ATP- and ubiquitin-independent manner. Among both proteasome pools, the immune proteasomes effectively produce antigen epitopes for MHC class I molecules and play a crucial role in the antitumor immunity. Excluding the immune proteasomes from their cells, numerous tumors avoid the immune system. On the contrary, tumor cells enhance the expression of the housekeeping proteasomes and 19S-subparticle. At this time, bortezomib, a patented proteasome inhibitor, is used as an anticancer therapy. This drug induces the cell cycle arrest and apoptosis of dividing tumor cells. However, bortezomib causes, firstly, deviations in immune functions, secondly, the increase of the housekeeping proteasome expression by a feedback mechanism. Taking into account the recent patents, we consider prospects of the development of new drugs directed to the regulation of the expression of the immune and housekeeping proteasomes and 19S-subparticle in tumor cells. .COPYRGT. 2008 Bentham Science Publishers

Ltd.

L10 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2006323217 MEDLINE <<LOGINID::20090630>>
DOCUMENT NUMBER: PubMed ID: 16552514
TITLE: Characterization and phylogenetic analysis of a cnidarian LMP X-like cDNA.
AUTHOR: Dishaw Larry J; Herrera Manuel L; Bigger Charles H
CORPORATE SOURCE: Department of Biological Sciences, Florida International University, Miami, FL, 33199, USA.
CONTRACT NUMBER: GM061347 (United States NIGMS NIH HHS)
SOURCE: Immunogenetics, (2006 Jun) Vol. 58, No. 5-6, pp. 454-64. Electronic Publication: 2006-03-22. Journal code: 0420404. ISSN: 0093-7711.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200608
ENTRY DATE: Entered STN: 2 Jun 2006 Last Updated on STN: 17 Aug 2006 Entered Medline: 16 Aug 2006

AB Proteasomes are multisubunit protease complexes which are partly responsible for metabolism of intracellular, ubiquitinylated proteins. Vertebrates have adapted a second and specialized structure responsible for the generation of peptides presented to the adaptive immune system and is thus, commonly referred to as the immunoproteasome. This complex is assembled from paralogous copies of subunits belonging to the constitutive, housekeeping proteasome. The immunoproteasome is more efficient in the generation of peptides for display on major histocompatibility complex (MHC) molecules. Important components of this complex are the paralogous members, LMP X and 7; where the latter replaces the former in the assembly of the immunoproteasome of vertebrates. In this report, we describe an LMP X-like cDNA from an endosymbiont-free gorgonian coral, Swiftia exserta. Cnidarians predate the phylogenetic divergence of protostomes and deuterostomes (P-D split), and are becoming an essential model for our comprehension of immune system evolution. Phylogenetic analyses of available sequences indicates that invertebrate LMP X-like sequences are outgroups to vertebrate LMP X and LMP 7, and is in agreement with previous observations that the duplication event giving rise to the two rapidly diverging lineages of proteasomal subunits occurred before jawed fished divergence.

L10 ANSWER 3 OF 3 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 1994320587 MEDLINE <<LOGINID::20090630>>
DOCUMENT NUMBER: PubMed ID: 8045254
TITLE: Displacement of housekeeping proteasome subunits by MHC-encoded LMPs: a newly discovered mechanism for modulating the multicatalytic proteinase complex.
AUTHOR: Fruh K; Gossen M; Wang K; Bujard H; Peterson P A; Yang Y
CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA 92037.
SOURCE: The EMBO journal, (1994 Jul 15) Vol. 13, No. 14, pp. 3236-44. Journal code: 8208664. ISSN: 0261-4189. Report No.: NLM-PMC395220.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

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FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199409
ENTRY DATE:         Entered STN: 9 Sep 1994
                    Last Updated on STN: 10 Dec 2002
                    Entered Medline: 1 Sep 1994
AB   The degradation of cytoplasmic antigens to peptides presented by class I
     MHC molecules is thought to be mediated by the ubiquitin/proteasome
     pathway.  Support for this view came from our observation that the subunit
     composition of proteasomes can be changed by interferon-gamma (IFN-gamma)
     treatment.  Thereby two subunits, LMP2 and LMP7, which are encoded in the
     MHC class II region, are incorporated into the proteasomal complex,
     whereas other subunits disappear.  In the experiments reported in this
     communication we studied the subunit changes occurring in cell lines where
     the expression of LMP2 or LMP7 can be regulated individually either by
     IFN-gamma induction or by applying a new system to control the expression
     of transfected LMPs.  In both situations LMP2 induction leads exclusively
     to the disappearance of housekeeping subunit 2, whereas LMP7 affects only
     subunit 10.  Subunit 2 was found to be 76% homologous to LMP2.  Since
     incorporation of LMP2 into the proteasomal complex prevents processing of
     the subunit 2 precursor, we conclude that LMP2 displaces subunit 2 during
     assembly.  Subunit displacement is most likely a general mechanism to
     modulate the catalytic activity of the proteasomal complex without
     changing its structure.  Furthermore, the controlled incorporation of
     transfected subunits into the complex offers a new approach to study
     proteasome function in vivo.


=> 26s-proteasome
26S-PROTEASOME IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s 26s-proteasome
L11       4573 26S-PROTEASOME

=> s t()cell or t()lymphocyte
=> s t()cell or t()lymphocyte
L12     632146 T(W) CELL OR T(W) LYMPHOCYTE

=> s l11 and l12
L13         55 L11 AND L12

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14          39 DUP REM L13 (16 DUPLICATES REMOVED)

=> d ibib abs 1-39

L14  ANSWER 1 OF 39  SCISEARCH  COPYRIGHT (c) 2009 The Thomson Corporation  on
     STN
ACCESSION NUMBER:    2009:702971  SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 453NK
TITLE:               Oxidized LDL Modulates Apoptosis of Regulatory T Cells in
                     Patients with ESRD
AUTHOR:              Meier, Pascal (Reprint)
CORPORATE SOURCE:    CHU Vaudois, Serv Nephrol, 17 Rue Bugnon, CH-1011
                     Lausanne, Switzerland (Reprint)
                     E-mail: pascal.meier@chuv.ch
AUTHOR:              Meier, Pascal (Reprint); Burnier, Michel
CORPORATE SOURCE:    CHU Vaudois, Serv Nephrol, CH-1011 Lausanne, Switzerland
```

E-mail: pascal.meier@chuv.ch
AUTHOR: Meier, Pascal (Reprint); Blanc, Edouard
CORPORATE SOURCE: Hop Sion, Div Nephrol, Dept Med, Sion, Switzerland
E-mail: pascal.meier@chuv.ch
AUTHOR: Golshayan, Dela; Pascual, Manuel
CORPORATE SOURCE: CHU Vaudois, Transplantat Ctr, CH-1011 Lausanne, Switzerland
AUTHOR: Golshayan, Dela; Pascual, Manuel
CORPORATE SOURCE: CHU Vaudois, Transplantat Immunopathol Lab, CH-1011 Lausanne, Switzerland
COUNTRY OF AUTHOR: Switzerland
SOURCE: JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, (JUN 2009) Vol. 20, No. 6, pp. 1368-1384.
ISSN: 1046-6673.
PUBLISHER: AMER SOC NEPHROLOGY, 1725 I ST, NW STE 510, WASHINGTON, DC 20006 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 45
ENTRY DATE: Entered STN: 18 Jun 2009
Last Updated on STN: 18 Jun 2009
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB increased levels of oxidized low-density lipoproteins (oxLDL) contribute to the increased risk for atherosclerosis, which persists even after adjusting for traditional risk factors, among patients with ESRD. Regulatory T cells (CD4(+)/CD25(+) Tregs), which down-regulate T cell responses to foreign and self-antigens, are protective in murine atherogenesis, but whether similar immunoregulation occurs in humans with ESRD is unknown. Because cellular defense systems against oxLDL involve proteolytic degradation, the authors investigated the role of oxLDL on proteasome activity of CD4(+)/CD25(+) Tregs in patients with ESRD. CD4(+)/CD25(+) Tregs isolated from uremic patients' peripheral blood, especially that of chronically hemodialyzed patients, failed to suppress cell proliferation, exhibited cell-cycle arrest, and entered apoptosis by altering proteasome activity. Treating CD4(+)/CD25(+) Tregs with oxLDL or uremic serum ex vivo decreased the number and suppressive capacity of CD4(+)/CD25(+) Tregs. In vitro, oxLDL promoted the accumulation of p27(kip1), the cycl in-dependent kinase inhibitor responsible for G(1) cell cycle arrest, and increased apoptosis in a time-and concentration-dependent manner. In summary, proteasome inhibition by oxLDL leads to cell cycle arrest and apoptosis, dramatically affecting the number and suppressive capacity of CD4(+)/CD25(+) Tregs in chronically hemodialyzed patients. This response may contribute to the immune dysfunction, microinflammation, and atherogenesis observed in patients with ESRD.

L14 ANSWER 2 OF 39 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2009402491 IN-PROCESS <<LOGINID::20090630>>
DOCUMENT NUMBER: PubMed ID: 19444310
TITLE: COP9 signalosome controls the Carma1-Bcl10-Malt1 complex upon T-cell stimulation.
AUTHOR: Welteke Verena; Eitelhuber Andrea; Duwel Michael; Schweitzer Katrin; Naumann Michael; Krappmann Daniel
CORPORATE SOURCE: Department Cellular Signal Integration, Helmholtz Zentrum Munchen-German Research Center for Environmental Health, Institute of Toxicology, Ingolstadter Landstrasse 1, Neuherberg 85764, Germany.
SOURCE: EMBO reports, (2009 Jun) Vol. 10, No. 6, pp. 642-8.
Electronic Publication: 2009-05-15.
Journal code: 100963049. E-ISSN: 1469-3178.
PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 10 Jun 2009
Last Updated on STN: 11 Jun 2009

AB The Carma1-Bcl10-Malt1 (CBM) complex connects T-cell receptor (TCR) signalling to the canonical IkappaB kinase (IKK)/NF (nuclear factor)-kappaB pathway. Earlier studies have indicated that the COP9 signalosome (CSN), a pleiotropic regulator of the ubiquitin/26S proteasome system, controls antigen responses in T cells. The CSN is required for the degradation of the NF-kappaB inhibitor IkappaBalpha, but other molecular targets involved in T-cell signalling remained elusive. Here, we identify the CSN subunit 5 (CSN5) as a new interactor of Malt1 and Carma1. T-cell activation triggers the recruitment of the CSN to the CBM complex, and CSN downregulation impairs TCR-induced IKK activation. Furthermore, the CSN is required for maintaining the stability of Bcl10 in response to T-cell activation. Taken together, our data provide evidence for a functional link between the evolutionarily conserved CSN and the adaptive immunoregulatory CBM complex in T cells.

L14 ANSWER 3 OF 39 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2009064615 EMBASE <<LOGINID::20090630>>
TITLE: Nonproteolytic Functions of Ubiquitin in Cell Signaling.
AUTHOR: Chen, Zhijian J. (correspondence); Sun, Lijun J.
CORPORATE SOURCE: Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX 75390-9148, United States. zhijian.chen@utsouthwestern.edu
AUTHOR: Chen, Zhijian J. (correspondence); Sun, Lijun J.
CORPORATE SOURCE: Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390-9148, United States. zhijian.chen@utsouthwestern.edu
SOURCE: Molecular Cell, (13 Feb 2009) Vol. 33, No. 3, pp. 275-286. Refs: 107
ISSN: 1097-2765 CODEN: MOCEFL
PUBLISHER: Cell Press, 1100 Massachusetts Avenue, Cambridge, MA 02138-9957, United States.
PUBLISHER IDENT.: S 1097-2765(09)00058-6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Feb 2009
Last Updated on STN: 24 Feb 2009

AB The small protein ubiquitin is a central regulator of a cell's life and death. Ubiquitin is best known for targeting protein destruction by the 26S proteasome. In the past few years, however, nonproteolytic functions of ubiquitin have been uncovered at a rapid pace. These functions include membrane trafficking, protein kinase activation, DNA repair, and chromatin dynamics. A common mechanism underlying these functions is that ubiquitin, or polyubiquitin chains, serves as a signal to recruit proteins harboring ubiquitin-binding domains, thereby bringing together ubiquitinated proteins and ubiquitin receptors to execute specific biological functions. Recent advances in understanding ubiquitination in protein kinase activation and DNA repair are discussed to illustrate the nonproteolytic functions of ubiquitin in cell signaling.

L14 ANSWER 4 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 2
ACCESSION NUMBER: 2008:1344496 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 368AS
TITLE: Fbxw7 in cell cycle exit and stem cell maintenance Insight from gene-targeted mice
AUTHOR: Nakayama, Keiichi I. (Reprint)
CORPORATE SOURCE: Kyushu Univ, Med Inst Bioregulat, Dept Mol & Cellular Biol, Higashi Ku, 3-1-1 Maidashi, Fukuoka 8128582, Japan (Reprint)
E-mail: nakayak1@bioreg.kyushu-u.ac.jp
AUTHOR: Nakayama, Keiichi I. (Reprint)
CORPORATE SOURCE: Kyushu Univ, Med Inst Bioregulat, Dept Mol & Cellular Biol, Higashi Ku, Fukuoka 8128582, Japan
E-mail: nakayak1@bioreg.kyushu-u.ac.jp
AUTHOR: Onoyama, Ichiro
CORPORATE SOURCE: Japan Sci & Technol Agcy, CREST, Saitama, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: CELL CYCLE, (1 NOV 2008) Vol. 7, No. 21, pp. 3307-3313. ISSN: 1538-4101.
PUBLISHER: LANDES BIOSCIENCE, 1002 WEST AVENUE, 2ND FLOOR, AUSTIN, TX 78701 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 53
ENTRY DATE: Entered STN: 5 Dec 2008
Last Updated on STN: 24 Dec 2008
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Regulation of the exit of cells from the cell cycle is important in the development of multicellular organisms and is also implicated in the maintenance of stem cells. Furthermore, defects in cell cycle exit are thought to be a major cause of cancer. However, the mechanisms responsible for regulation of cell cycle exit have remained largely unknown. Fbxw7 is the F-box protein subunit of an SCF-type ubiquitin ligase complex that targets positive regulators of the cell cycle-including cyclin E, c-Myc, Notch and c-Jun-for ubiquitylation and subsequent degradation by the 26S proteasome in order to promote cell cycle exit. Consistent with such a function, mutations of the Fbxw7 gene have been detected in various human malignancies. We have recently generated conventional and conditional Fbxw7 knockout mice and examined stem cells, progenitor cells and differentiated cells in the mutant animals for cell cycle defects. Here we summarize the pleiotropic phenotypes of Fbxw7 deficiency in various cell types including T cells, hematopoietic stem cells and embryonic fibroblasts. Such phenotypes have provided insight into the biological roles of Fbxw7 in cell cycle exit, stem cell maintenance and oncosuppression.

L14 ANSWER 5 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2008:699182 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 301VU
TITLE: Proteasome inhibition suppresses essential immune functions of human CD4(+) T cells
AUTHOR: Naujokat, Cord (Reprint)
CORPORATE SOURCE: Univ Heidelberg, Inst Immunol, Dept Transplantat Immunol, Neuenheimer Feld 305, D-69120 Heidelberg, Germany (Reprint)
AUTHOR: Berges, Carsten; Haberstock, Heinrich; Fuchs, Dominik; Miltz, Marion; Sadeghi, Mahmoud; Opelz, Gerhard; Daniel, Volker
CORPORATE SOURCE: Univ Heidelberg, Inst Immunol, Dept Transplantat Immunol,

D-69120 Heidelberg, Germany
E-mail: cord.naujokat@med.uni-heidelberg.de
COUNTRY OF AUTHOR: Germany
SOURCE: IMMUNOLOGY, (JUN 2008) Vol. 124, No. 2, pp. 234-246. ISSN: 0019-2805.
PUBLISHER: BLACKWELL PUBLISHING, 9600 GARSINGTON RD, OXFORD OX4 2DQ, OXON, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 69
ENTRY DATE: Entered STN: 5 Jun 2008
Last Updated on STN: 12 Jun 2008

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The proteasome constitutes the central proteolytic component of the highly conserved ubiquitin-proteasome system, which is required for the maintenance and regulation of basic cellular processes, including differentiation, proliferation, cell cycling, gene transcription and apoptosis. Here we show that inhibition of proteasomal proteolytic activity by the proteasome inhibitors bortezomib and lactacystin suppresses essential immune functions of human CD4(+) T cells activated by allogeneic dendritic cells (DCs). In activated CD4(+) T cells, proteasome inhibition induces apoptosis accompanied by rapid accumulation and stabilization of the tumour suppressor protein p53. Activated CD4(+) T cells surviving proteasome inhibition undergo inhibition of proliferation by induction of G(1) phase cell-cycle arrest. Induction of G(1) arrest is accompanied by the accumulation of cyclin-dependent kinase inhibitors p21(WAF1/CIP1) and p27(KIP1) and the disappearance of cyclin A, cyclin D2 and proliferating cell nuclear antigen, proteins known to regulate G(1) to S phase cell-cycle transitions. Expression of the activation-associated cell surface receptors CD25, CD28, CD120b and CD134 as well as production of interferon-gamma (IFN-gamma), tumour necrosis factor-alpha (TNF-alpha), interleukin-4 (IL-4) and IL-5 is suppressed in response to proteasome inhibition in CD4(+) T cells activated by DCs. Expression of CD25, IFN-gamma, TNF-alpha, IL-4 and IL-5 is known to be mediated by the transcriptional activity of nuclear factor of activated T cells (NFAT), and we show here that proteasome inhibition suppresses activation and nuclear translocation of NFATc2 in activated CD4(+) T cells. Thus, the proteasome is required for essential immune functions of activated CD4(+) T cells and can be defined as a molecular target for the suppression of deregulated and unwanted T-cell-mediated immune responses.

L14 ANSWER 6 OF 39 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2009004843 EMBASE <<LOGINID::20090630>>
TITLE: Multiple forms of proteasomes and their role in tumor fate.
AUTHOR: Sharova, Natalie (correspondence); Zakharova, Liudmila
CORPORATE SOURCE: N.K. Koltsov Institute of Developmental Biology, Russian Academy of Sciences, Vavilova St. 26, Moscow 119334, Russian Federation. npsharova@bk.ru
SOURCE: Recent Patents on Endocrine, Metabolic and Immune Drug Discovery, (2008) Vol. 2, No. 3, pp. 152-161.
Refs: 97
ISSN: 1872-2148
PUBLISHER: Bentham Science Publishers B.V., P.O. Box 294, Bussum, 1400 AG, Netherlands.
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry

030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jan 2009
Last Updated on STN: 30 Jan 2009

AB Mammalian and human cells contain multiple forms of proteasomes different in their structure and functions. 26S-proteasome pool regulates most cellular processes through ATP- and ubiquitin-dependent hydrolysis of proteins participating in these processes. This function is possible due to 19S-subparticle capable to recognize ubiquitinated proteins, unfold and direct them into the proteolytic chamber. 20S-proteasome pool is capable to degrade some damaged and foreign proteins in an ATP- and ubiquitin-independent manner. Among both proteasome pools, the immune proteasomes effectively produce antigen epitopes for MHC class I molecules and play a crucial role in the antitumor immunity. Excluding the immune proteasomes from their cells, numerous tumors avoid the immune system. On the contrary, tumor cells enhance the expression of the housekeeping proteasomes and 19S-subparticle. At this time, bortezomib, a patented proteasome inhibitor, is used as an anticancer therapy. This drug induces the cell cycle arrest and apoptosis of dividing tumor cells. However, bortezomib causes, firstly, deviations in immune functions, secondly, the increase of the housekeeping proteasome expression by a feedback mechanism. Taking into account the recent patents, we consider prospects of the development of new drugs directed to the regulation of the expression of the immune and housekeeping proteasomes and 19S-subparticle in tumor cells. .COPYRGT. 2008 Bentham Science Publishers Ltd.

L14 ANSWER 7 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2008:31272 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 238KK
TITLE: Enhanced expression of interferon-gamma-induced antigen-processing machinery components in a spontaneously occurring cancer
AUTHOR: Cascio, Paolo (Reprint)
CORPORATE SOURCE: Univ Turin, Sch Vet Med, Dept Vet Morphophysiol, Via Leonardo Vinci 44, I-10095 Grugliasco, Italy (Reprint)
AUTHOR: Cerruti, Fulvia; Martano, Marina; Petterino, Claudio; Bollo, Enrico; Morello, Emanuela; Bruno, Renato; Buracco, Paolo
CORPORATE SOURCE: Univ Turin, Dept Vet Morphophysiol, Grugliasco, Italy; Univ Turin, Dept Anim Pathol, Grugliasco, Italy; Univ Padua, Dept Publ Hlth, Legnaro, Italy
E-mail: paolo.cascio@unito.it
COUNTRY OF AUTHOR: Italy
SOURCE: NEOPLASIA, (NOV 2007) Vol. 9, No. 11, pp. 960-969. ISSN: 1522-8002.
PUBLISHER: NEOPLASIA PRESS, 1150 W MEDICAL CENTER DR, MSRB III, RM 9303, ANN ARBOR, MI 48109-0648 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 48
ENTRY DATE: Entered STN: 10 Jan 2008
Last Updated on STN: 10 Jan 2008

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In human tumors, changes in the surface expression and/or function of major histocompatibility complex (MHC) class I antigens are frequently found and may provide malignant cells with a mechanism to escape control

of the immune system. This altered human lymphocyte antigen (HLA) class I phenotype can be caused by either structural alterations or dysregulation of genes encoding subunits of HLA class I antigens and/or components of the MHC class I antigen-processing machinery (APM). Herein we analyze the expression of several proteins involved in the generation of MHC class I epitopes in feline injection site sarcoma, a spontaneously occurring tumor in cats that is an informativemodel for the study of tumor biology in other species, including humans. Eighteen surgically removed primary fibrosarcoma lesions were analyzed, and an enhanced expression of two catalytic subunits of immunoproteasomes, PA28 and leucine aminopeptidase, was found in tumors compared to matched normal tissues. As a functional counterpart of these changes in protein levels, proteasomal activities were increased in tissue extracts from fibrosarcomas. Taken together, these results suggest that alterations in the APM system may account for reduced processing of selected tumor antigens and may potentially provide neoplastic fibroblasts with a mechanism for escape from T-cell recognition and destruction.

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ACCESSION NUMBER: 2007501953 EMBASE <<LOGINID::20090630>>

TITLE: Use of novel proteosome inhibitors as a therapeutic strategy in lymphomas current experience and emerging concepts.

AUTHOR: Jacobs, Peter (correspondence)

CORPORATE SOURCE: The Department of Haematology, Bone Marrow Transplant Unit, The Searll Research Laboratory for Cellular and Molecular Biology, Burnham Road, Plumstead 7800 Cape Town, South Africa. haematol@icon.co.za

AUTHOR: Jacobs, Peter (correspondence)

CORPORATE SOURCE: College of Medicine, University of Nebraska Medical Centre, United States. haematol@icon.co.za

AUTHOR: Abayomi, Emmanuel Akinola; Sissolak, Gerhard; Jacobs, Peter (correspondence)

CORPORATE SOURCE: Faculty of Health Sciences, Stellenbosch University - Tygerberg Academic Hospital, South Africa. haematol@icon.co.za

SOURCE: Transfusion and Apheresis Science, (Aug 2007) Vol. 37, No. 1, pp. 85-92.
Refs: 30
ISSN: 1473-0502 CODEN: TASRCE

PUBLISHER IDENT.: S 1473-0502(07)00100-0

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 15 Nov 2007
Last Updated on STN: 15 Nov 2007

AB Precedent from preclinical experiments coupled with two pivotal phase 2 studies in myeloma has focused attention on a potential role for ubiquitin-proteasome pathway in modulating a number of events that occur commonly in the neoplastic process involving proteins in the regulation of cells cycling, growth and differentiation. This influence is vested in the proteasomes which are large complexes of proteolytic enzymes responsible for degradation of many of these intracellular messengers. Logically interest has centred on molecules having the capacity to influence, by degradation, such molecules and although a number of agents

are in development bortezomib is the only one currently in clinical use. Velcade, formerly PS-341, is a novel dipeptide boronic acid capable of reversibly inhibiting the 26S proteasome through a range of activities. The latter are anti-proliferative and proapoptotic with the latter blocking nuclear transcription via NF-κ B in addition to down regulating adhesion and inhibiting angiogenesis. Additional changes are mediated in protein folding within the endoplasmic reticulum and contribute to cell death. These concepts are given focus by considering their introduction into treatment of lymphoreticular malignancy. .COPYRGT. 2007.

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ACCESSION NUMBER:	20072230754 EMBASE <<LOGINID::20090630>>
TITLE:	Molecular targeting in pancreatic cancer.
AUTHOR:	Wadler, Scott, Prof. (correspondence)
CORPORATE SOURCE:	Department of Hematology and Medical Oncology, Weill Medical College, Cornell University, 1300 York Avenue, New York, NY 10021, United States. scw2004@med.cornell.edu
AUTHOR:	Wadler, Scott, Prof. (correspondence)
CORPORATE SOURCE:	Weill Medical College, Cornell University, 1300 York Avenue, New York, NY 10021, United States. scw2004@med.cornell.edu
SOURCE:	Reviews on Recent Clinical Trials, (Jan 2007) Vol. 2, No. 1, pp. 69-75. Refs: 33 ISSN: 1574-8871
COUNTRY:	United Kingdom
DOCUMENT TYPE:	Journal; General Review; (Review)
FILE SEGMENT:	016 Cancer 030 Clinical and Experimental Pharmacology 037 Drug Literature Index 038 Adverse Reactions Titles 048 Gastroenterology
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 11 Jun 2007 Last Updated on STN: 11 Jun 2007

AB The mortality and morbidity of tumors of the upper GI tract are formidable with incidence and mortality nearly the same. Therefore, better therapies are necessary, and these are generally molecularly targeted therapies. This chapter focuses on the treatment of pancreatic cancer with targeted therapy. Important cellular pathways are reviewed, including signal transduction, proteasome inhibition, cell cycle, anti-angiogenesis pathways, immunologic therapies, viral therapy, epigenetic therapies and microarray analysis. Signal transduction pathways include epidermal growth factor receptors, such as cetuximab and Tarceva, as well as other less well-defined pathways. Proteasome inhibition includes inhibition of the 26S proteasome with PS-341. Cell cycle therapies include inhibitors of all the proteins involved in pushing the cell through the cell cycle. Viral therapies mainly cover the adenoviruses, like ONYX-015, and Reolysin, a type 3 serotype Dearing strain with little pathogenicity. Immunological therapies include cytokines, vaccines and cell-based therapies. Epigenetic therapies are mainly centered around histone deacetylases. Microarray analysis analyzes expression of thousands of genes to create a tumor profile, mainly for prognosis or prediction. Various promising treatment strategies are reviewed in terms of treatment with molecularly-guided therapies. Complications of therapy, particularly rash and thrombosis are reviewed. .COPYRGT. 2007 Bentham Science Publishers Ltd.

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ACCESSION NUMBER: 2007003429 EMBASE <<LOGINID::20090630>>
TITLE: Bortezomib as an antitumor agent.
AUTHOR: Roccaro, A.M.; Vacca, A.; Dammacco, F.
CORPORATE SOURCE: Department of Internal Medicine and Oncology, University of Bari Medical School, Bari, Italy.
AUTHOR: Ribatti, D. (correspondence)
CORPORATE SOURCE: Department of Human Anatomy and Histology, University of Bari Medical School, Bari, Italy. ribatti@anatomia.uniba.it
AUTHOR: Hideshima, T.; Richardson, P.G.; Anderson, K.C.
CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, United States.
AUTHOR: Roccaro, A.M.; Russo, D.
CORPORATE SOURCE: Unit of Blood Diseases and Cell Therapy, University of Brescia Medical School, Brescia, Italy.
SOURCE: Current Pharmaceutical Biotechnology, (Dec 2006) Vol. 7, No. 6, pp. 441-448.
Refs: 72
ISSN: 1389-2010 E-ISSN: 1873-4316 CODEN: CPBUBP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
025 Hematology
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Feb 2007
Last Updated on STN: 16 Feb 2007

AB The ubiquitin-proteasome pathway (UPP) is the major non-lysosomal proteolytic system in the cytosol and nucleus of all eukaryotic cells. Bortezomib (also known as PS-341 and Velcade ®) is a proteasome inhibitor, a novel class of cancer therapies. Bortezomib blocks multi-ubiquitinated protein degradation by inhibiting 26S proteasome activity, including regulating cell cycle, anti-apoptosis, and inflammation, as well as immune surveillance. In multiple myeloma (MM) cells, bortezomib directly induces cell stress response followed by activation of c-Jun NH(2) terminal kinase (JNK)/ stress-activated protein kinase (SAPK), and triggers caspase-dependent apoptosis of tumor cells. Recent clinical studies demonstrated that bortezomib had remarkable anti-tumor activity in refractory and relapsed MM, providing the basis to approval by FDA. Its anti-tumor activities earlier in the course, in combination therapies, and in other malignancies is ongoing. .COPYRGT. 2006 Bentham Science Publishers Ltd.

L14 ANSWER 11 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 3

ACCESSION NUMBER: 2006:26137 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 997EK
TITLE: Differential effects of proteasome inhibitors on cell cycle and apoptotic pathways in human YT and Jurkat cells
AUTHOR: Goldfarb R H (Reprint)
CORPORATE SOURCE: Sopher Therapeut Inc, 100 Overlook Ctr Suite 100, Princeton, NJ 08540 USA (Reprint)
AUTHOR: Lu M; Dou Q P; Kitson R P; Smith D M
CORPORATE SOURCE: Sopher Therapeut Inc, Princeton, NJ 08540 USA; Univ N Texas, Hlth Sci Ctr, Inst Canc Res, Dept Mol Biol &

Immunol, Ft Worth, TX 76107 USA; Univ S Florida, Coll Med, H Lee Moffitt Canc Ctr & Res Inst, Drug Discovery Program, Tampa, FL 33612 USA
E-mail: rgoldfarb@sopherion.com

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, (1 JAN 2006) Vol. 97, No. 1, pp. 122-134.
ISSN: 0730-2312.

PUBLISHER: WILEY-LISS, DIV JOHN WILEY & SONS INC, 111 RIVER ST, HOBOKEN, NJ 07030 USA.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 54

ENTRY DATE: Entered STN: 11 Jan 2006
Last Updated on STN: 11 Jan 2006

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Herein, we report differential effects of various proteasome inhibitors including clasto-lactacystin-beta-lactone, (-)-epigallocatechin gallate (EGCG) and N-Acetyl-Leu-Leu-Norleu-al (LLnL) on proteasomal activities of YT and Jurkat cells, human natural killer (NK) and T cell lines, respectively. The inhibitory rates of these inhibitors on the purified 20S proteasomal and 26S proteasornal chyrnotrypsin-like activity in whole cell extracts and intact cells did not show significant differences between the two cell lines. The viability of both cell lines was reduced in the presence of LLnL. Subsequent studies revealed a reduction of the mitochondrial membrane potential and caspase-3 activation in these two cell lines upon treatment with proteasome inhibitors; however, caspase-3 activation occurred Much earlier in Jurkat cells. Cell cycle analysis indicated a sub-G, apoptotic cell Population in Jurkat cells and G(2)/M arrest in YT cells after they were treated by proteasome inhibitors. Moreover, pretreatment of YT cells by a caspase inhibitor followed by a proteasome inhibitor did not increase the percentage of G(2)/M phase cells. in addition, accumulation of p27 and I kappa B-alpha was detected only in Jurkat cells, but not YT cells. In summary, proteasome inhibitors may act differentially in cell cycle arrest and apoptosis Of tumors of NK and T cell origin, and may have similar effects oil normal NK and T cells.

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ACCESSION NUMBER: 2006622419 EMBASE <<LOGINID::20090630>>

TITLE: Proteasomal chymotrypsin-like peptidase activity is required for essential functions of human monocyte-derived dendritic cells.

AUTHOR: Naujokat, Cord, Dr. (correspondence); Berges, Carsten; Hoh, Alexandra; Wieczorek, Hubert; Fuchs, Dominik; Ovens, Jorg; Miltz, Marion; Sadeghi, Mahmoud; Opelz, Gerhard; Daniel, Volker

CORPORATE SOURCE: Department of Transplantation Immunology, Institute of Immunology, University of Heidelberg, Heidelberg, Germany. cord.naujokat@med.uni-heidelberg.de; volker.daniel@med.uni-heidelberg.de

SOURCE: Immunology, (2006) Vol. 120, No. 1, pp. 120-132.
Refs: 51
ISSN: 0019-2805 E-ISSN: 1365-2567 CODEN: IMMUAM

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 9 Jan 2007
Last Updated on STN: 9 Jan 2007

AB The ubiquitin-proteasome pathway is the principal system for extralysosomal protein degradation in eukaryotic cells, and is essential for the regulation and maintenance of basic cellular processes, including differentiation, proliferation, cell cycling, gene transcription and apoptosis. The 26S proteasome, a large multicatalytic protease complex, constitutes the system's proteolytic core machinery that exhibits different proteolytic activities residing in defined proteasomal subunits. We have identified proteasome inhibitors - bortezomib, epoxomicin and lactacystin - which selectively inhibit the proteasomal β5 subunit-located chymotrypsin-like peptidase activity in human monocyte-derived dendritic cells (DCs). Inhibition of proteasomal chymotrypsin-like peptidase activity in immature and mature DCs impairs the cell-surface expression of CD40, CD86, CD80, human leucocyte antigen (HLA)-DR, CD206 and CD209, induces apoptosis, and impairs maturation of DCs, as demonstrated by decreased cell-surface expression of CD83 and lack of nuclear translocation of RelA and RelB. Inhibition of chymotrypsin-like peptidase activity abrogates macropinocytosis and receptor-mediated endocytosis of macromolecular antigens in immature DCs, and inhibits the synthesis of interleukin (IL)-12p70 and IL-12p40 in mature DCs. As a functional consequence, DCs fail to stimulate allogeneic CD4(+) and CD8(+) T cells and autologous CD4(+) T cells sufficiently in response to inhibition of chymotrypsin-like peptidase activity. Thus, proteasomal chymotrypsin-like peptidase activity is required for essential functions of human DCs, and inhibition of proteasomal chymotrypsin-like peptidase activity by selective inhibitors, or by targeting β5 subunit expression, may provide a novel therapeutic strategy for suppression of deregulated and unwanted immune responses. .COPYRGT. 2006 Blackwell Publishing Ltd.

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ACCESSION NUMBER: 2006:209407 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: BDS55
TITLE: The use of mass spectrometry to identify antigens from proteasome processing
AUTHOR: Burlet-Schiltz O (Reprint)
CORPORATE SOURCE: CNRS, Inst Pharmacol & Biol Stuct, Toulouse, France (Reprint)
AUTHOR: Claverol S; Gairin J E; Monsarrat B
CORPORATE SOURCE: Univ Victor Segalen Bordeaux, Bordeaux, France; CNRS, Inst Sci Technol Medicament Toulouse, Toulouse, France
COUNTRY OF AUTHOR: France
SOURCE: MASS SPECTROMETRY: MODIFIED PROTEINS AND GLYCOCONJUGATES, (2005) Vol. 405, pp. 264-300.
ISSN: 0076-6879.
PUBLISHER: ELSEVIER ACADEMIC PRESS INC, 525 B STREET, SUITE 1900, SAN DIEGO, CA 92101-4495 USA.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 125
ENTRY DATE: Entered STN: 2 Mar 2006
Last Updated on STN: 10 Aug 2006
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Mass spectrometry (MS) is a powerful tool for the characterization of antigenic peptides that play a major role in the immune system. Most of the major histocompatibility complex (MHC) class I peptides are generated during the degradation of intracellular proteins by the proteasome, a catalytic complex present in all eukaryotic cells. This chapter focuses on the contribution of MS to the understanding of the mechanisms of

antigen processing by the proteasome. This knowledge may be valuable for the design of specific inhibitors of proteasome, which has recently been recognized as a therapeutic target in cancer therapies and for the development of efficient peptidic vaccines in immunotherapies. Examples from the literature have been chosen to illustrate how MS data can contribute first to the understanding of the mechanisms of proteasomal processing and, second, to the understanding of the crucial role of proteasome in cytotoxic T lymphocytes (CTL) activation. The general strategy based on MS analyses used in these studies is also described.

L14 ANSWER 14 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:324506 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 906IE
TITLE: Corticosterone impairs MHC class I antigen presentation by dendritic cells via reduction of peptide generation
AUTHOR: Truckenmiller M E (Reprint)
CORPORATE SOURCE: Penn State Univ, Coll Med, Dept Microbiol & Immunol, Milton S Hershey Med Ctr, Hershey, PA 17033 USA (Reprint)
AUTHOR: Princiotta M F; Norbury C C; Bonneau R H
CORPORATE SOURCE: NIAID, Viral Dis Lab, Bethesda, MD 20892 USA
E-mail: met11@psu.edu
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF NEUROIMMUNOLOGY, (MAR 2005) Vol. 160, No. 1-2, pp. 48-60.
ISSN: 0165-5728.
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 58
ENTRY DATE: Entered STN: 31 Mar 2005
Last Updated on STN: 31 Mar 2005

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The presentation of viral peptide-MHC class I complexes by antigen presenting cells, such as dendritic cells (DCs), is obligatory for the generation of antiviral effector and memory CD8(+) cytotoxic T lymphocyte (CTL) responses. Prolonged psychological stress is immunosuppressive and undermines primary and memory CTL-mediated antiviral immunity; however, the mechanisms involved are unknown. Using a panel of novel reagents and techniques, we quantitatively measured the effect of the stress-induced hormone corticosterone (CORT) on the efficiency of DCs to process and present virally expressed antigen, characterized the conditions for this CORT-inediated effect, and delineated the components of the MHC class I pathway that were affected. We found that physiologically relevant levels of CORT, prior to infection and acting via the glucocorticoid receptor, suppressed the formation of peptide-MHC class I complexes on the Surface of infected DCs. We further showed that this suppression of peptide-MHC class I complexes is via the action of CORT on elements of the class I pathway upstream from TAP that are involved in the generation of antigenic peptides. This CORT-mediated suppression of peptide-class I complexes on DCs also resulted in a marked reduction of their ability to activate a specific T cell hybridoma.
These findings offer a mechanism contributing to the stress-induced suppression of host defenses against viral diseases and have implications for the efficacy of antiviral vaccines. At the most fundamental cellular level, this impairment of antigen processing has implications for the regulation of protein degradation in all cells, which is critical to many aspects of immune function. (c) 2004 Elsevier B.V. All rights reserved.

L14 ANSWER 15 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on

STN
ACCESSION NUMBER: 2005:973063 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 966UR
TITLE: Interferon-gamma, the functional plasticity of the ubiquitin-proteasome system, and MHC class I antigen processing
AUTHOR: Kloetzel P M (Reprint)
CORPORATE SOURCE: Berlin Univ, Charite, Inst Biochem, Monbijoustr 2, D-10117 Berlin, Germany (Reprint)
AUTHOR: Strehl B; Seifert U; Kruger E; Heink S; Kuckelkorn U
CORPORATE SOURCE: Berlin Univ, Charite, Inst Biochem, D-10117 Berlin, Germany
E-mail: p-m.kloetzel@charite.de
COUNTRY OF AUTHOR: Germany
SOURCE: IMMUNOLOGICAL REVIEWS, (OCT 2005) Vol. 207, pp. 19-30. ISSN: 0105-2896.
PUBLISHER: BLACKWELL PUBLISHING, 9600 GARSINGTON RD, OXFORD OX4 2DQ, OXON, ENGLAND.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 95
ENTRY DATE: Entered STN: 6 Oct 2005
Last Updated on STN: 6 Oct 2005

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The proteasome system is a central component of a cascade of proteolytic processing steps required to generate antigenic peptides presented at the cell surface to cytotoxic T lymphocytes by major histocompatibility complex (MHC) class I molecules. The nascent protein pool or DRiPs (defective ribosomal products) appear to represent an important source for MHC class I epitopes. Owing to the destructive activities of aminopeptidases in the cytosol, at most 1% of the peptides generated by the ubiquitin-proteasome system seems to be made available to the immune system. Interferon-gamma (IFN-gamma) helps to override these limitations by the formation of immunoproteasomes, the activator complex PA28, and the induction of several aminopeptidases. Both immunoproteasomes and PA28 use cleavage sites already used by constitutive proteasomes but with altered and in some cases dramatically enhanced frequency. Therefore, two proteolytic cascades appear to have evolved to provide MHC class I epitopes. The 'constitutive proteolytic cascade' is designed to efficiently degrade proteins to single amino acid residues, allowing only a small percentage of peptides to be presented at the cell surface. In contrast, the IFN-gamma-controlled proteolytic cascade generates larger amounts of appropriate antigenic peptides, assuring more peptides to overcome the proteolytic restrictions of the constitutive system, thereby enhancing MHC class I antigen presentation.

L14 ANSWER 16 OF 39 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005466834 EMBASE <<LOGINID::20090630>>
TITLE: Preclinical evaluation of the proteasome inhbitor bortezomib in cancer therapy.
AUTHOR: Boccadoro, Mario (correspondence)
CORPORATE SOURCE: Section of Hematology, University of Torino, Torino, Italy. mario.boccadoro@unito.it
AUTHOR: Morgan, Gareth
CORPORATE SOURCE: Royal Marsden Hospital, Surrey, United Kingdom. gareth.morgan@rmh.nthames.nhs.uk
AUTHOR: Cavenagh, Jaime
CORPORATE SOURCE: St. Bartholomew's Hospital, Department of Haematology, London, United Kingdom. j.d.cavenagh@qmul.ac.uk
SOURCE: Cancer Cell International, (1 Jun 2005) Vol. 5. arn. 18.

Refs: 64
ISSN: 1475-2867 E-ISSN: 1475-2867 CODEN: CCIACC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Nov 2005
Last Updated on STN: 3 Nov 2005

AB Bortezomib is a highly selective, reversible inhibitor of the 26S proteasome that is indicated for single-agent use in the treatment of patients with multiple myeloma who have received at least 2 prior therapies and are progressing on their most recent therapy. Clinical investigations have been completed or are under way to evaluate the safety and efficacy of bortezomib alone or in combination with chemotherapy in multiple myeloma, both at relapse and presentation, as well as in other cancer types. The antiproliferative, proapoptotic, antiangiogenic, and antitumor activities of bortezomib result from proteasome inhibition and depend on the altered degradation of a host of regulatory proteins. Exposure to bortezomib has been shown to stabilize p21, p27, and p53, as well as the proapoptotic Bid and Bax proteins, caveolin-1, and inhibitor κB-α, which prevents activation of nuclear factor κB-induced cell survival pathways. Bortezomib also promoted the activation of the proapoptotic c-Jun-NH2 terminal kinase, as well as the endoplasmic reticulum stress response. The anticancer effects of bortezomib as a single agent have been demonstrated in xenograft models of multiple myeloma, adult T-cell leukemia, lung, breast, prostate, pancreatic, head and neck, and colon cancer, and in melanoma. In these preclinical in vivo studies, bortezomib treatment resulted in decreased tumor growth, angiogenesis, and metastasis, as well as increased survival and tumor apoptosis. In several in vitro and/or in vivo cancer models, bortezomib has also been shown to enhance the antitumor properties of several antineoplastic treatments. Importantly, bortezomib was generally well tolerated and did not appear to produce additive toxicities when combined with other therapies in the dosing regimens used in these preclinical in vivo investigations. These findings provide a rationale for further clinical trials using bortezomib alone or in combination regimens with chemotherapy, radiation therapy, immunotherapy, or novel agents in patients with hematologic malignancies or solid tumors.

L14 ANSWER 17 OF 39 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2006590294 EMBASE <<LOGINID::20090630>>
TITLE: Constitutive degradation of IKBα in human T lymphocytes is mediated by calpain.
AUTHOR: Ponnappan, Subramaniam; Ponnappan, Usha (correspondence)
CORPORATE SOURCE: Department of Geriatrics, University of Arkansas for Medical Sciences, Little Rock, AR, United States. sponnappan@uams.edu; uponnappan@uams.edu
AUTHOR: Cullen, Sarah J.; Ponnappan, Usha (correspondence)
CORPORATE SOURCE: Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR, United States. uponnappan@uams.edu; scullen@uams.edu
AUTHOR: Ponnappan, Subramaniam; Ponnappan, Usha (correspondence)
CORPORATE SOURCE: VA Medical Research, Central Arkansas Veterans Health Care System, Little Rock, AR, United States. sponnappan@uams.edu ; uponnappan@uams.edu
SOURCE: Immunity and Ageing, (4 Nov 2005) Vol. 2. arn. 15.

Refs: 20
ISSN: 1742-4933
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Dec 2006
Last Updated on STN: 29 Dec 2006

AB Background: Activation-induced induction of transcription factor NFκB in T lymphocytes is regulated by its inhibitor IκBα. NFκB activation has been demonstrated to occur either by phosphorylation on serine residues 32 and 36 of the inhibitor, IκBα, followed by ubiquitination and degradation of the inhibitor by the 26S proteasome, or by a proteasome-independent mechanism involving tyrosine phosphorylation, but not degradation. However, the mechanism underlying constitutive regulation of the levels of the inhibitor, IκB, in primary human T lymphocytes, remains to be fully delineated. Results: We demonstrate here, the involvement of a proteasome-independent pathway for constitutive regulation of IκBα levels in primary human T lymphocytes. Pretreatment with a cell permeable calpain inhibitor, E64D, but not with a proteasome specific inhibitor, lactacystin, blocks stimulus-independent IκBα degradation in primary human T cells. However, E64D pre-treatment fails to impact on IκBα levels following stimulation with either TNFα or pervanadate. Other isoforms of the inhibitor, IκBβ, and IκBγ, appear not to be subject to a similar ligand-independent regulation. Unlike the previously reported decline in ligand-induced degradation of IκBα in T cells from the elderly, constitutive degradation does not exhibit an age-associated decline, demonstrating proteasome-independent regulation of the activity. Conclusion: Our studies support a role for an E64D sensitive protease in regulating constitutive levels of IκBα in T cells, independent of the involvement of the 26S proteasome, and suggests a biological role for constitutive degradation of IκBα in T cells. .COPYRGT. 2005 Ponnappan et al; licensee BioMed Central Ltd.

L14 ANSWER 18 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:964923 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 863DM
TITLE: Stable ubiquitination of human T-cell leukemia virus type 1 tax is required for proteasome binding
AUTHOR: Pique C (Reprint)
CORPORATE SOURCE: Hop St Louis, Inst Univ Hematol, CNRS UPR 9051, 1 Ave Claude Vellefaux, F-75010 Paris, France (Reprint)
AUTHOR: Chiari E; Lamsoul I; Lodewick J; Chopin C; Bex F
CORPORATE SOURCE: Hop St Louis, Inst Univ Hematol, CNRS UPR 9051, F-75010 Paris, France; Free Univ Brussels, Microbiol Lab, Brussels, Belgium
E-mail: pique@chu-stlouis.fr
COUNTRY OF AUTHOR: France; Belgium
SOURCE: JOURNAL OF VIROLOGY, (NOV 2004) Vol. 78, No. 21, pp. 11823-11832.
ISSN: 0022-538X.
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA.
DOCUMENT TYPE: Article; Journal

LANGUAGE: English
REFERENCE COUNT: 41
ENTRY DATE: Entered STN: 25 Nov 2004
Last Updated on STN: 25 Nov 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Human T-cell leukemia virus type 1 (HTLV-1) is the retrovirus responsible for adult T-cell leukemia and HTLV-1-associated myelopathy. Adult T-cell leukemia development is mainly due to the ability of the viral oncoprotein Tax to promote T-cell proliferation, whereas the appearance of HTLV-1-associated myelopathy involves the antigenic properties of Tax. Understanding the events regulating the intracellular level of Tax is therefore an important issue. How Tax is degraded has not been determined, but it is known that Tax binds to proteasomes, the major sites for degradation of intracellular proteins, generally tagged through polyubiquitin conjugation. In this study, we investigated the relationship between Tax, ubiquitin, and proteasomes. We report that mono- and polyubiquitinated Tax proteins can be recovered from both transfected 293T cells and T lymphocytes. We also show that lysine residues located in the carboxy-terminal domain of Tax are the principal targets of this process. Remarkably, we further demonstrate that mutation of lysine residues in the C-terminal part of Tax, which massively reduces Tax ubiquitination, impairs proteasome binding, and conversely, that a Tax mutant that binds poorly to this particle (M22) is faintly ubiquitinated, suggesting that Tax ubiquitination is required for association with cellular proteasomes. Finally, we document that comparable amounts of ubiquitinated species were found whether proteasome activities were inhibited or not, providing evidence that they are not directly addressed to proteasomes for degradation. These findings indicate that although it is ubiquitinated and binds to proteasomes, Tax is not massively degraded via the ubiquitin-proteasome pathway and therefore reveal that Tax conjugation to ubiquitin mediates a nonproteolytic function.

L14 ANSWER 19 OF 39 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004539302 MEDLINE <<LOGINID::20090630>>
DOCUMENT NUMBER: PubMed ID: 15494532
TITLE: Green tea epigallocatechin-3-gallate mediates T cellular NF-kappa B inhibition and exerts neuroprotection in autoimmune encephalomyelitis.
AUTHOR: Aktas Orhan; Prozorovski Timour; Smorodchenko Alina; Savaskan Nicolai E; Lauster Roland; Kloetzel Peter-Michael; Infante-Duarte Carmen; Brocke Stefan; Zipp Frauke
CORPORATE SOURCE: Institute of Neuroimmunology, Neuroscience Research Center, Charite, Berlin, Germany.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2004 Nov 1) Vol. 173, No. 9, pp. 5794-800.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 30 Oct 2004
Last Updated on STN: 19 Dec 2004
Entered Medline: 24 Nov 2004

AB Recent studies in multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis (EAE), point to the fact that even in the early phase of inflammation, neuronal pathology plays a pivotal role in the sustained disability of affected individuals. We show that the major green tea constituent, (-)-epigallocatechin-3-gallate (EGCG), dramatically

suppresses EAE induced by proteolipid protein 139-151. EGCG reduced clinical severity when given at initiation or after the onset of EAE by both limiting brain inflammation and reducing neuronal damage. In orally treated mice, we found abrogated proliferation and TNF-alpha production of encephalitogenic T cells. In human myelin-specific CD4+ T cells, cell cycle arrest was induced, down-regulating the cyclin-dependent kinase 4. Interference with both T cell growth and effector function was mediated by blockade of the catalytic activities of the 20S/26S proteasome complex, resulting in intracellular accumulation of IkappaB-alpha and subsequent inhibition of NF-kappaB activation. Because its structure implicates additional antioxidative properties, EGCG was capable of protecting against neuronal injury in living brain tissue induced by N-methyl-D-aspartate or TRAIL and of directly blocking the formation of neurotoxic reactive oxygen species in neurons. Thus, a natural green tea constituent may open up a new therapeutic avenue for young disabled adults with inflammatory brain disease by combining, on one hand, anti-inflammatory and, on the other hand, neuroprotective capacities.

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ACCESSION NUMBER: 2004:894677 SCISEARCH <<LOGINID::20090630>>

THE GENUINE ARTICLE: 858UH

TITLE: Human immunodeficiency virus type 1 protease inhibitors block toll-like receptor 2 (TLR2)- and TLR4-induced NF-kappa B activation

AUTHOR: Equils O (Reprint)

CORPORATE SOURCE: Cedars Sinai Med Ctr, Ahmanson Dept Pediat, Div Pediat Infect Dis, Steven Spielberg Pediat Res Ctr, 8700 Beverly Rd, Room 4220, Los Angeles, CA 90048 USA (Reprint)

AUTHOR: Shapiro A; Madak Z; Liu C R; Lu D N

CORPORATE SOURCE: Cedars Sinai Med Ctr, Ahmanson Dept Pediat, Div Pediat Infect Dis, Steven Spielberg Pediat Res Ctr, Los Angeles, CA 90048 USA; Univ Calif Los Angeles, David Geffen Sch Med, Dept Mol & Med Pharmacol, Los Angeles, CA USA; Univ Calif Los Angeles, Mattel Childrens Hosp, Div Pediat Infect Dis, Los Angeles, CA USA
E-mail: ozlem.equils@cshs.org

COUNTRY OF AUTHOR: USA

SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (OCT 2004) Vol. 48, No. 10, pp. 3905-3911.
ISSN: 0066-4804.

PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 64

ENTRY DATE: Entered STN: 5 Nov 2004
Last Updated on STN: 5 Nov 2004

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Coinfections with opportunistic and pathogenic bacteria induce human immunodeficiency virus (HIV) replication through microbial antigen activation of NF-kappaB. Here, we assessed whether HIV type 1 protease inhibitors (PI) block microbial antigen activation of NF-kappaB. Human microvessel endothelial cells were transiently transfected with either endothelial cell-leukocyte adhesion molecule NF-kappaB luciferase or interleukin 6 (IL-6) promoter luciferase constructs by using FuGENE 6, and they were treated with PI (nelfinavir, ritonavir, or saquinavir) prior to stimulation with the Toll-like receptor 4 (TLR4) and TLR2 ligands, with lipopolysaccharide (LPS), soluble Mycobacterium tuberculosis factor, or Staphylococcus epidermidis phenol-soluble modulin, respectively, or with

tumor necrosis factor alpha (TNF-alpha). Luciferase activity was measured by using a Promega luciferase kit. TNF-alpha release from the supernatant was measured by enzyme-linked immunosorbent assay. Cell death was assessed by lactate dehydrogenase assay. We observed that PI pretreatment blocked the TLR2- and TLR4- as well as the TNF-alpha-mediated NF-kappaB activation, in a dose-dependent manner. PI pretreatment also blocked the LPS-induced IL-6 promoter transactivation and TNF-alpha secretion. These data suggest that PI block HIV replication not only by inhibiting the HIV protease but also by blocking the TLR- and TNF-alpha-mediated NF-kappaB activation and proinflammatory cytokine production. These findings may help explain the immunomodulatory effects of PI, and they suggest an advantage for PI-containing drug regimens in the treatment of HIV-infected patients who are coinfected with opportunistic and pathogenic bacteria.

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ACCESSION NUMBER: 2004119481 EMBASE <<LOGINID::20090630>>
TITLE: Arecoline Tripeptide Inhibitors of Proteasome.
AUTHOR: Marastoni, Mauro (correspondence); Baldisserotto, Anna; De Risi, Carmela; Pollini, Gian Piero; Tomatis, Roberto
CORPORATE SOURCE: Dept. Pharmaceut. Sci./Biotech. Ctr., University of Ferrara, I-44100 Ferrara, Italy. mru@unife.it
AUTHOR: Canella, Alessandro; Gavioli, Riccardo
CORPORATE SOURCE: Dept. of Biochem. and Molec. Biology, University of Ferrara, I-44100 Ferrara, Italy.
AUTHOR: Marastoni, Mauro (correspondence)
CORPORATE SOURCE: Dipto. di Scienze Farmaceutiche, Universita di Ferrara, Via Fossato di Mortara 17-19, I-44100 Ferrara, Italy. mru@unife.it
SOURCE: Journal of Medicinal Chemistry, (11 Mar 2004) Vol. 47, No. 6, pp. 1587-1590.
Refs: 21
ISSN: 0022-2623 CODEN: JMCMAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Apr 2004
Last Updated on STN: 12 Apr 2004

AB The 26S proteasome is a multicatalytic protease complex that plays an essential role in intracellular protein degradation. We have synthesized and tested a series of arecoline peptide derivatives where the peptide portion derives from a screening of tripeptide sequences, and the arecoline moiety has been considered as a potential substrate for catalytic threonine. Derivatives 17-19 are the best compounds of the series, showing chymotryptic-like (β5) inhibition (IC(50) 1 μM) and favorable pharmacokinetic properties.

L14 ANSWER 22 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:627040 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 833IO
TITLE: Generation of major histocompatibility complex class I antigens: functional interplay between proteasomes and TPPII
AUTHOR: Kloetzel P M (Reprint)
CORPORATE SOURCE: Humboldt Univ, Univ Med Sch Charite, Monbijoustr 2, D-10117 Berlin, Germany (Reprint)
AUTHOR: Kloetzel P M (Reprint)

CORPORATE SOURCE: Humboldt Univ, Univ Med Sch Charite, D-10117 Berlin, Germany
E-mail: p-m.kloetzel@charite.de
COUNTRY OF AUTHOR: Germany
SOURCE: NATURE IMMUNOLOGY, (JUL 2004) Vol. 5, No. 7, pp. 661-669. ISSN: 1529-2908.
PUBLISHER: NATURE PUBLISHING GROUP, 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707 USA.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 102
ENTRY DATE: Entered STN: 29 Jul 2004
Last Updated on STN: 29 Jul 2004

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The proteasome is key in the cascade of proteolytic processing required for the generation of peptides presented at the cell surface to cytotoxic T lymphocytes by major histocompatibility complex class I molecules. Proteasome-dependent epitope processing is greatly improved through the interferon-gamma-induced formation of immunoproteasomes and the activator complex PA28. Tripeptidyl aminopeptidase II also has a strong effect on epitope generation. With its endoproteolytic and exoproteolytic activities, TPPII acts `downstream' of the proteasome and relies on products released by the proteasome. The antigen-processing cascade involving different proteolytic systems raises anew the question of how antigenic peptides are generated. We therefore revisit the interferon-gamma-induced immune adaptation of the proteasome and attempt to redefine its function in connection with the emerging importance of TPPII.

L14 ANSWER 23 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 5
ACCESSION NUMBER: 2005:81766 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 886FZ
TITLE: The proteasorne and MHC class I antigen processing
AUTHOR: Kloetzel P M (Reprint)
CORPORATE SOURCE: Humboldt Univ, Inst Biochem, Charite, Fak Med, Monbijoust 2, D-10117 Berlin, Germany (Reprint)
AUTHOR: Kloetzel P M (Reprint)
CORPORATE SOURCE: Humboldt Univ, Inst Biochem, Charite, Fak Med, D-10117 Berlin, Germany
E-mail: p-m.kloetzel@charite.de
COUNTRY OF AUTHOR: Germany
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH, (29 NOV 2004) Vol. 1695, No. 1-3, pp. 225-233. ISSN: 0167-4889.
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 111
ENTRY DATE: Entered STN: 3 Feb 2005
Last Updated on STN: 3 Feb 2005

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB By generating peptides from intracellular antigens, which are then presented to T cells, the ubiquitin/26S proteasome system plays a central role in the cellular immune response. Under the control of interferon-gamma the proteolytic properties of the proteasome are adapted to the requirements of the immune system. Interferon-gamma induces the formation of immunoproteasomes and the synthesis of the proteasome activator PA28. Both alter the proteolytic properties of the proteasome complex and enhance proteasomal function in antigen

presentation. Thus. a combination of several of regulatory events tunes the proteasome system for maximal efficiency in the generation of MHC class I antigens. (C) 2004 Published by Elsevier B.V.

L14 ANSWER 24 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 6
ACCESSION NUMBER: 2004:630656 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 835DK
TITLE: Inhibition of the proteasome reduces transfer-induced diabetes in nonobese diabetic mice
AUTHOR: Hoglund P (Reprint)
CORPORATE SOURCE: Karolinska Inst, Ctr Microbiol & Tumor Biol, Box 280, S-17177 Stockholm, Sweden (Reprint)
AUTHOR: Petrovic J; Hall H; Mehr R; Glas R
CORPORATE SOURCE: Karolinska Inst, Ctr Microbiol & Tumor Biol, S-17177 Stockholm, Sweden; Bar Ilan Univ, Fac Life Sci, Ramat Gan, Israel; Huddinge Univ Hosp, Karolinska Inst, Ctr Infect Med, Dept Med, Stockholm, Sweden
E-mail: petter.hoglund@mtc.ki.se
COUNTRY OF AUTHOR: Sweden; Israel
SOURCE: SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (AUG 2004) Vol. 60, No. 1-2, pp. 134-142.
ISSN: 0300-9475.
PUBLISHER: BLACKWELL PUBLISHING LTD, 9600 GARSINGTON RD, OXFORD OX4 2DG, OXON, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 34
ENTRY DATE: Entered STN: 29 Jul 2004
Last Updated on STN: 29 Jul 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Inhibition of the 26S proteasome reduces the severity of several immune-mediated diseases. Here, we report that the proteasome also regulates transfer-induced diabetes in nonobese mice. Treatment of recipient mice with the proteasome inhibitor N-alpha-benzyloxycarbonyl-l-leucyl-l-leucyl-l-leucinal (MG132) resulted in a 76% reduction in transfer-induced diabetes. The closely related inhibitor carbobenzoxy-l-leucyl-l-leucinal that inhibits calpains but not the proteasome had no protective effect, suggesting that MG132 acted via inhibition of the proteasome. MG132 decreased proliferation of transferred T cells in the pancreatic lymph nodes in vivo and prevented their expansion in a dose-dependent manner in vitro, consistent with a direct effect by MG132 on the T cells. MG132 did not prevent migration of transferred T cells into the islets but reduced the number of mice with severe infiltration. We suggest that MG132 prevents transfer-induced diabetes by directly targeting the autoreactive T cells and lowering their diabetogenic potential.

L14 ANSWER 25 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:64328 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: BY09Y
TITLE: The components of the proteasome system and their role in MHC class I antigen processing
AUTHOR: Kloetzel P M (Reprint)
CORPORATE SOURCE: Humboldt Univ, Charite, Inst Biochem, Fak Med, Monbijoust 2, D-10117 Berlin, Germany (Reprint)
AUTHOR: Kruger E; Kuckelkorn U; Sijts A
CORPORATE SOURCE: Humboldt Univ, Charite, Inst Biochem, Fak Med, D-10117 Berlin, Germany
COUNTRY OF AUTHOR: Germany

SOURCE: REVIEWS OF PHYSIOLOGY, BIOCHEMISTRY AND PHARMACOLOGY, VOL 148, (2004) Vol. 148, pp. 81-104.
ISSN: 0303-4240.
PUBLISHER: SPRINGER-VERLAG BERLIN, HEIDELBERGER PLATZ 3, D-14197 BERLIN, GERMANY.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 161
ENTRY DATE: Entered STN: 23 Jan 2004
Last Updated on STN: 23 Jan 2004
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB By generating peptides from intracellular antigens which are then presented to T cells, the ubiquitin/26S proteasome system plays a central role in the cellular immune response. The proteolytic properties of the proteasome are adapted to the requirements of the immune system by proteasome components whose synthesis is under the control of interferon-gamma. Among these are three subunits with catalytic sites that are incorporated into the enzyme complex during its de novo synthesis. Thus, the proteasome assembly pathway and the formation of immunoproteasomes play a critical regulatory role in the regulation of the proteasome's catalytic properties. In addition, interferon-gamma also induces the synthesis of the proteasome activator PA28 which, as part of the so-called hybrid proteasome, exerts a more selective function in antigen presentation. Consequently, the combination of a number of regulatory events tunes the proteasome system to gain maximal efficiency in the generation of peptides with regard to their quality and quantity.

L14 ANSWER 26 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:868332 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 727XL
TITLE: Tyrosine residues direct the ubiquitination and degradation of the NY-1 hantavirus G1 cytoplasmic tail
AUTHOR: Mackow E R (Reprint)
CORPORATE SOURCE: SUNY Stony Brook, Dept Med, HSC T17, Rm 60, Stony Brook, NY 11794 USA (Reprint)
AUTHOR: Geimonen E; Fernandez I; Gavrilovskaya I N
CORPORATE SOURCE: SUNY Stony Brook, Dept Med, Stony Brook, NY 11794 USA; SUNY Stony Brook, Dept Mol Genet & Microbiol, Stony Brook, NY 11794 USA; SUNY Stony Brook, Mol Cell Biol Program, Stony Brook, NY 11794 USA; Northport VA Med Ctr, Northport, NY 11768 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF VIROLOGY, (OCT 2003) Vol. 77, No. 20, pp. 10760-10768.
ISSN: 0022-538X.
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 67
ENTRY DATE: Entered STN: 17 Oct 2003
Last Updated on STN: 17 Oct 2003
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The hantavirus G1 protein contains a long C-terminal cytoplasmic tail of 142 residues. Hantavirus pulmonary syndrome-associated hantaviruses contain conserved tyrosine residues near the C terminus of G1 which form an immunoreceptor tyrosine activation motif (ITAM) and interact with Src and Syk family kinases. During studies of the G1 ITAM we observed that fusion proteins containing the G1 cytoplasmic tail were poorly expressed.

Expression of G1 cytoplasmic tail constructs were dramatically enhanced by treating cells with the proteasome inhibitor ALLN, suggesting that the protein is ubiquitinated and degraded via the 26S proteasome. By using a 6-His-tagged ubiquitin, we demonstrated that the G1 cytoplasmic tail is polyubiquitinated and degraded in the absence of proteasome inhibitors. Expression of only the ITAM-containing domain also directed protein ubiquitination and degradation in the absence of upstream residues. Deleting the C-terminal 51 residues of G1, including the ITAM, stabilized G1 and blocked polyubiquitination and degradation of the protein. Site-directed mutagenesis of both ITAM tyrosines (Y619 and Y632) to phenylalanine also blocked polyubiquitination of G1 proteins and dramatically enhanced G1 protein stability. In contrast, the presence of Y627, which is not part of the ITAM motif, had no effect on G1 stability. Mutagenesis of just Y619 enhanced G1 stability, inhibited G1 ubiquitination, and increased the half-life of G1 by threefold. Mutating only Y632 had less of an effect on G1 protein stability, although Y619 and Y632 synergistically contributed to G1 instability. These findings suggest that Y619, which is conserved in all hantaviruses, is the primary signal for directing G1 ubiquitination and degradation. Collectively these findings indicate that specific conserved tyrosines within the G1 cytoplasmic tail direct the polyubiquitination and degradation of expressed G1 proteins and provide a potential means for down-regulating hantavirus G1 surface glycoproteins and cellular proteins that interact with G1.

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ACCESSION NUMBER:	2003405340 EMBASE <<LOGINID::20090630>>
TITLE:	HIV-1 Vif blocks the antiviral activity of APOBEC3G by impairing both its translation and intracellular stability.
AUTHOR:	Stopak, Kim; De Noronha, Carlos; Yonemoto, Wes; Greene, Warner C. (correspondence)
CORPORATE SOURCE:	Gladstone Inst. of Virol./Immunology, Univ. of California, San Francisco, San Francisco, CA 94143, United States. wgreene@gladstone.ucsf.edu
AUTHOR:	Greene, Warner C. (correspondence)
CORPORATE SOURCE:	Depts. of Med., Microbiol./Immunol., Univ. of California, San Francisco, San Francisco, CA 94143, United States. wgreene@gladstone.ucsf.edu
SOURCE:	Molecular Cell, (1 Sep 2003) Vol. 12, No. 3, pp. 591-601. Refs: 30 ISSN: 1097-2765 CODEN: MOCEFL
COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article
FILE SEGMENT:	026 Immunology, Serology and Transplantation 029 Clinical and Experimental Biochemistry 004 Microbiology: Bacteriology, Mycology, Parasitology and Virology
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 23 Oct 2003 Last Updated on STN: 23 Oct 2003

AB The human immunodeficiency virus type 1 (HIV-1) relies on Vif (viral infectivity factor) to overcome the potent antiviral function of APOBEC3G (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G, also known as CEM15). Using an APOBEC3G-specific antiserum, we now show that Vif prevents virion incorporation of endogenous APOBEC3G by effectively depleting the intracellular levels of this enzyme in HIV-1-infected T cells. Vif achieves this depletion by both impairing the translation of APOBEC3G mRNA and accelerating the posttranslational degradation of the APOBEC3G protein by the 26S proteasome. Vif

physically interacts with APOBEC3G, and expression of Vif alone in the absence of other HIV-1 proteins is sufficient to cause depletion of APOBEC3G. These findings highlight how the bimodal translational and posttranslational inhibitory effects of Vif on APOBEC3G combine to markedly suppress the expression of this potent antiviral enzyme in virally infected cells, thereby effectively curtailing the incorporation of APOBEC3G into newly formed HIV-1 virions.

L14 ANSWER 28 OF 39 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2002050740 MEDLINE <<LOGINID::20090630>>
DOCUMENT NUMBER: PubMed ID: 11772523
TITLE: Ubiquitin-proteasome pathway is compromised in CD45RO+ and CD45RA+ T lymphocyte subsets during aging.
AUTHOR: Ponnappan Usha
CORPORATE SOURCE: Department of Microbiology, University of Arkansas for Medical Sciences, CAVHS, GC 143, 151/LRVA, John L. McClellan Memorial VA Hospital, 4300 West 7th Street, Little Rock, AR 72205, USA.. ponnappanusha@uams.edu
CONTRACT NUMBER: M01 RR 14288 (United States NCRR NIH HHS)
R01 AG 13081 (United States NIA NIH HHS)
SOURCE: Experimental gerontology, (2002 Jan-Mar) Vol. 37, No. 2-3, pp. 359-67.
Journal code: 0047061. ISSN: 0531-5565.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 25 Apr 2002
Entered Medline: 24 Apr 2002

AB Recent reports from our laboratory have demonstrated that CD45RO+ and CD45RA+ T lymphocytes from the elderly are compromised in their response to activation-induced IL-2 receptor expression, IkappaB-alpha degradation, as well as nuclear translocation of NFkB. To understand the basis of this activation-induced dysfunction in the elderly, we have examined the role of the ubiquitin-proteasome pathway. Our results demonstrate that both CD45RO+ and CD45RA+ T lymphocytes from the elderly show significant reduction in the constitutive 26S proteasome -associated chymotryptic activity, when compared to those in the young. Additionally, anti-CD3-CD28 treatment induced enhancement of proteasome-associated enzymatic activity in cells from the young, but not in cells from the elderly. Lowered proteasome-associated activity and its effect on reduced immune responses in the elderly could be mimicked by experiments which involved pretreatment of T cells from young donors with a proteasome specific inhibitor, lactacystin. These data demonstrate that IL-2 receptor induction is clearly compromised in T cells from the young when proteasomes are inhibited by pretreatment with lactacystin. An examination of ubiquitin specific hydrolase activity, demonstrated a decrease in activated CD45RA+ and CD45RO+ T cell subsets from the elderly when compared to young. These results suggest that lowered proteasome-associated enzymatic activity in combination with compromised de-ubiquitinating activity may be responsible for lowered activation-induced NFkB and NFkB-mediated gene expression in elderly subjects.

L14 ANSWER 29 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:707538 SCISEARCH <<LOGINID::20090630>>

THE GENUINE ARTICLE: 584KF
TITLE: Remodelling of the S3 PA700 proteasome activator gene chromatin structure during thymocyte differentiation
AUTHOR: Antoniou A N (Reprint)
CORPORATE SOURCE: Univ Dundee, Wellcome Trust Bioctr, Div Cell Biol & Immunol, Dundee DD1 5EH, Scotland (Reprint)
AUTHOR: Moore N; Dyson P J
CORPORATE SOURCE: AstraZeneca, Macclesfield SK10 4TG, Cheshire, England; Hammersmith Hosp, Transplantat Biol Grp, Ctr Clin Sci, London W12 0NN, England
COUNTRY OF AUTHOR: Scotland; England
SOURCE: IMMUNOGENETICS, (JUL 2002) Vol. 54, No. 4, pp. 260-267. ISSN: 0093-7711.
PUBLISHER: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41
ENTRY DATE: Entered STN: 13 Sep 2002
Last Updated on STN: 13 Sep 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The proteasome is the major cytosolic protease, composed of a 20S catalytic core that associates with either the 19S (PA700) activator or the 11S (PA28) regulator complex. The 19S complex is thought to promote protein substrate unfolding and subsequent degradation, but precise functions for the individual subunits remain undefined. The chromatin structure and regulation of the S3 (P91A) subunit of the 19S activator was examined as a novel approach towards understanding its role in the complex. DNase I hypersensitivity (HS) analysis of S3 chromatin revealed a ubiquitous DNase I HS site mapping to the promoter region. Examination of the S3 chromatin structure in thymocytes, a dynamic population that undergo substantial proliferation, apoptosis, and differentiation, revealed an additional DNase I HS site mapping to the sixth intron of the genomic sequence. This second site was demonstrated to be associated with CD4+CD8+ double-positive (DP) but not CD4+ single-positive (SP) thymoma cell lines, and may correlate with a downregulation of S3 message. When a DP thymic cell line was induced to differentiate through retroviral transduction with Notch-1, the second DNase I HS site was dramatically diminished, illustrating that S3 chromatin is developmentally regulated during thymocyte positive selection.

L14 ANSWER 30 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:840154 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 601PN
TITLE: To DRiP or not to DRiP: generating peptide ligands for MHC class I molecules from biosynthesized proteins
AUTHOR: Yewdell J (Reprint)
CORPORATE SOURCE: NIAID, Viral Dis Lab, Room 211 Bldg 4, 4 Ctr Dr, Bethesda, MD 20892 USA (Reprint)
AUTHOR: Yewdell J (Reprint)
CORPORATE SOURCE: NIAID, Viral Dis Lab, Bethesda, MD 20892 USA
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR IMMUNOLOGY, (OCT 2002) Vol. 39, No. 3-4, pp. 139-146.
ISSN: 0161-5890.
PUBLISHER: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 75
ENTRY DATE: Entered STN: 1 Nov 2002

Last Updated on STN: 1 Nov 2002

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ACCESSION NUMBER: 2002371151 EMBASE <<LOGINID::20090630>>
TITLE: Ubiquitin-dependent proteolysis: Its role in human diseases and the design of therapeutic strategies.
AUTHOR: Sakamoto, Kathleen M (correspondence)
CORPORATE SOURCE: Department of Pediatrics and Department of Pathology, Division of HematologyOncology, Gwynne Hazen Cherry Memorial Laboratories, 10833 Le Conte Avenue, Los Angeles, CA 90095-1752, United States. kms@ucla.edu
AUTHOR: Sakamoto, Kathleen M (correspondence)
CORPORATE SOURCE: Division of Biology, California Institute of Technology, United States. kms@ucla.edu
AUTHOR: Sakamoto, Kathleen M (correspondence)
CORPORATE SOURCE: Department of Pediatrics, Mattel Children's Hospital, David Geffen Sch. of Med. at UCLA, 10833 Le Conte Avenue, Los Angeles, CA 90095-1752, United States. kms@ucla.edu
SOURCE: Molecular Genetics and Metabolism, (2002) Vol. 77, No. 1-2, pp. 44-56.
Refs: 107
ISSN: 1096-7192 CODEN: MGMEFF
PUBLISHER IDENT.: S 1096-7192(02)00146-4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 Nov 2002
Last Updated on STN: 7 Nov 2002

AB Protein degradation is one of the tactics employed by the cell for irreversibly inactivating proteins. In eukaryotes, ATP-dependent protein degradation in the cytoplasm and nucleus is carried out by the 26S proteasome. Most proteins are targeted to the 26S proteasome by covalent attachment of a multi-ubiquitin chain. A key component of the enzyme cascade that results in attachment of the multi-ubiquitin chain to the target or labile protein is the ubiquitin ligase that controls the specificity of the ubiquitination reaction. Defects in ubiquitin-dependent proteolysis have been shown to result in a variety of human diseases, including cancer, neurodegenerative diseases, and metabolic disorders. This review focuses on the role of ubiquitin-dependent degradation in human disease and potential clinical applications that are being developed to exploit the cells natural proteolytic machinery to treat diseases. .COPYRGT. 2002 Published by Elsevier Science (USA).

L14 ANSWER 32 OF 39 MEDLINE on STN DUPLICATE 8

ACCESSION NUMBER: 2001541125 MEDLINE <<LOGINID::20090630>>
DOCUMENT NUMBER: PubMed ID: 11588135
TITLE: Tannic acid potently inhibits tumor cell proteasome activity, increases p27 and Bax expression, and induces G1 arrest and apoptosis.
AUTHOR: Nam S; Smith D M; Dou Q P
CORPORATE SOURCE: Drug Discovery Program, H. Lee Moffitt Cancer Center & Research Institute, and Interdisciplinary Oncology Program and Department of Biochemistry & Molecular Biology, College of Medicine, University of South Florida, Tampa, Florida 33612, USA.
SOURCE: Cancer epidemiology, biomarkers & prevention : a

publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, (2001 Oct) Vol. 10, No. 10, pp. 1083-8.
Journal code: 9200608. ISSN: 1055-9965.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 8 Oct 2001
Last Updated on STN: 22 Jan 2002
Entered Medline: 4 Dec 2001

AB Animal studies have demonstrated that a dietary polyphenol known as tannic acid (TA) exhibits anticarcinogenic activity in chemically induced cancers, although the involved molecular target remains unknown. In addition, proteasome inhibitors have been shown to suppress human tumor growth in nude mice. Most recently, we have reported that ester-bond-containing tea polyphenols are potent proteasome inhibitors in vitro and in vivo. We have hypothesized that TA, which contains multiple similar gallate moieties linked by ester bonds, should inhibit the proteasome activity. Here, we report that indeed TA potently and specifically inhibits the chymotrypsin-like activity of purified 20S proteasome (IC(50) = 0.06 microg/ml), 26S proteasome of Jurkat T-cell extracts, and 26S proteasome of living Jurkat cells. Inhibition of the proteasome by TA in Jurkat cells results in accumulation of two natural proteasome substrates, the cyclin-dependent kinase inhibitor p27(Kip1) and the proapoptotic protein Bax, followed by growth arrest in G1 and induction of apoptotic cell death. Our present study suggests that TA targets and inhibits the proteasome in tumor cells, which may contribute to the previously observed anticarcinogenic activity of TA.

L14 ANSWER 33 OF 39 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:264238 SCISEARCH <<LOGINID::20090630>>
THE GENUINE ARTICLE: 412RW
TITLE: At the crossroads of cell biology and immunology: DRiPs and other sources of peptide ligands for MHC class I molecules
AUTHOR: Yewdell J W (Reprint)
CORPORATE SOURCE: NIAID, Viral Dis Lab, Bethesda, MD 20892 USA (Reprint)
AUTHOR: Schubert U; Bennink J R
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF CELL SCIENCE, (MAR 2001) Vol. 114, No. 5, pp. 845-851.
ISSN: 0021-9533.
PUBLISHER: COMPANY OF BIOLOGISTS LTD, BIDDER BUILDING CAMBRIDGE COMMERCIAL PARK COWLEY RD, CAMBRIDGE CB4 4DL, CAMBS, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 47
ENTRY DATE: Entered STN: 6 Apr 2001
Last Updated on STN: 6 Apr 2001

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB CD8(+) T cells are a critical element of vertebrate immune responses to viruses and other intracellular parasites. They roam the body, monitoring cells for the presence of foreign peptides associated with MHC

class I molecules of the major histocompatibility complex (MHC), Although it is clear that most of these peptides are generated through the action of proteasomes, the nature of the substrates degraded by proteasomes is an open question. Recent findings indicate that the major pool of substrates consists of a heterogeneous subset of proteins that are degraded within minutes of their synthesis. Evidence suggests that the fraction of newly synthesized proteins targeted for destruction is remarkably high - 30% or more, depending on cell type - possibly because they are defective in some way and cannot reach their intended conformation or location cellular in a time frame deemed appropriate by cells.

L14 ANSWER 34 OF 39 MEDLINE on STN
ACCESSION NUMBER: 2000501841 MEDLINE <<LOGINID::20090630>>
DOCUMENT NUMBER: PubMed ID: 11048297
TITLE: [The proteasome and malignant hemopathies]. Proteasome et hemopathies malignes.
AUTHOR: Lavabre-Bertrand T; Henry L; Guiraud I; Carillo S; Bureau J P
CORPORATE SOURCE: Laboratoire de Biologie Cellulaire et de Cytogenetique Moleculaire. Faculte de Medecine de Montpellier-Nimes, France.. t-lavabre@usa.net
SOURCE: Morphologie : bulletin de l'Association des anatomistes, (2000 Jun) Vol. 84, No. 265, pp. 39-43. Ref: 29 Journal code: 9814314. ISSN: 1286-0115.
PUB. COUNTRY: France
DOCUMENT TYPE: (ENGLISH ABSTRACT) Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 22 Mar 2001 Last Updated on STN: 22 Mar 2001 Entered Medline: 21 Nov 2000

AB Proteasomes are the main non lysosomal proteolytic structures of the cells. They correspond to the major system eliminating abnormal proteins, short half-life proteins and proteins controlling the cell cycle. They are essential for the production of peptides subsequently presented by the MHC-I. They are formed by a proteolytic core (the 20S proteasome) made of 4 rings of 7 proteic subunits associated with regulatory complexes (namely the 19S complex forming the 26S proteasome). Using classical cell biology techniques (cytometry, immunofluorescence microscopy, Western blot) our group has particularly studied the proteasome expression of leukaemic cell lines (U937 and CCRF-CEM) during in vitro differentiation induced by PMA and Vitamin D plus retinoic acid. During differentiation, the level of proteasome expression and its localization vary. The various monoclonal antibodies used provided different patterns according to the different subunits. There was a general trend to a disappearance of nuclear proteasome and to a decrease in their cytoplasmic expression. In contrast, proteosomal antigens were increased on the cell membrane and in culture supernatants. We derived an ELISA test to measure plasma proteasome concentrations. Preliminary results showed differences between patients with haemopoietic malignancies or solid tumors and normal donors. Proteasome levels varied under treatment. They were correlated with LDH levels. Taken together, these results argue in favor of a role for cellular proteasomes in malignant differentiation process, and emphasize the qualitative changes in proteasome expression. Plasma proteasomes do not only reflect tumor cell mass and could play a role in addition to their proteolytic activity. They seem to be a relevant tool for diagnosis, prognosis and therapeutic monitoring.

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ACCESSION NUMBER: 1999050068 EMBASE <<LOGINID::20090630>>
TITLE: Proteasome participates in the alteration of signal transduction in T and B lymphocytes following trauma-hemorrhage.
AUTHOR: Samy, T.S. Anantha; Schwacha, Martin G.; Chung, Chun-Shiang; Cioffi, William G.; Bland, Kirby I.; Chaudry, Irshad H. (correspondence)
CORPORATE SOURCE: Center for Surgical Research, Department of Surgery, Brown University School of Medicine, 593 Eddy Street, Providence, RI 02903, United States. ichaudry@lifespan.org
SOURCE: Biochimica et Biophysica Acta - Molecular Basis of Disease, (6 Jan 1999) Vol. 1453, No. 1, pp. 92-104.
Refs: 44
ISSN: 0925-4439 CODEN: BBADEX
PUBLISHER IDENT.: S 0925-4439(98)00089-1
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 25 Feb 1999
Last Updated on STN: 25 Feb 1999

AB Proteasomes are essential components of the cellular protein degradation machinery. They are nonlysosomal and their participation is critical for (1) the removal of short lived proteins involved in metabolic regulation and cell proliferation, (2) the control of the activities of regulators involved in gene transcription, such as nuclear factor-κB (NF-κB) and signal transducer and activator of transcription (STAT1), and (3) processing of antigenic peptides for MHC class I presentation. Trauma-hemorrhage induces profound immunosuppression which is characterized by reduced splenocyte proliferation, interleukin (IL)-2 and interferon (IFN)-γ productive capacity, increased activation of transcription factors NF-κB and STAT1 in splenic T lymphocytes, reduced macrophage antigen presentation capacity and inordinate release of proinflammatory cytokines, such as IL-6 and tumor necrosis factor-α. Furthermore, it appears that the activity of several regulatory proteins involved in immune function is altered by trauma-hemorrhage. Since proteasomes are involved in regulation and removal of regulatory proteins, we hypothesized that trauma-hemorrhage alters proteasomal activity in splenic lymphocytes. The data showed that activities of 26s proteasome from CD3(+)CD4(+) and CD3(+)CD8(+) splenic T lymphocytes were enhanced following trauma-hemorrhage which was associated with increased expression of NF-κB and STAT1. On the other hand, trauma-hemorrhage attenuated the activity of 26s proteasome from splenic B lymphocytes which was restored upon IFN-γ stimulation and correlated with increased expression of NF-κB. These studies indicate a potential role for proteasomes in the regulation of signal transduction in splenic T and B lymphocytes following trauma-hemorrhage, and also suggest them as potential therapeutic targets for attenuation of immune suppression associated with this form of injury. Copyright (C) 1999 Elsevier Science B.V.

L14 ANSWER 36 OF 39 MEDLINE on STN DUPLICATE 9

ACCESSION NUMBER: 1998078704 MEDLINE <<LOGINID::20090630>>
DOCUMENT NUMBER: PubMed ID: 9418895
TITLE: Expression of constitutively active IkappaB beta in T cells of transgenic mice: persistent NF-kappaB activity is

required for T-cell immune responses.
AUTHOR: Attar R M; Macdonald-Bravo H; Raventos-Suarez C; Durham S K; Bravo R
CORPORATE SOURCE: Department of Oncology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-4000, USA.
SOURCE: Molecular and cellular biology, (1998 Jan) Vol. 18, No. 1, pp. 477-87.
Journal code: 8109087. ISSN: 0270-7306.
Report No.: NLM-PMC121517.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 30 Jan 1998
Last Updated on STN: 30 Jan 1998
Entered Medline: 22 Jan 1998

AB The transcription factor NF-kappaB is normally sequestered in the cytoplasm by members of the IkappaB family, including IkappaB alpha, IkappaB beta, and the recently cloned IkappaB epsilon. Upon cellular activation, these inhibitors are rapidly phosphorylated on two amino-terminal serines, ubiquitinated, and degraded by the 26S proteasome, releasing a functional NF-kappaB. To determine the importance of IkappaB beta in NF-kappaB regulation in T cells, we generated transgenic mice expressing a constitutively active IkappaB beta mutant (mIkappaB beta) under the control of the lck promoter. The transgene contains the two critical N-terminal serine residues mutated to alanines and therefore no longer susceptible to degradation upon cell activation. mIkappaB beta is unable to totally displace IkappaB alpha from RelA-containing complexes, thus allowing a transient activation of NF-kappaB upon T-cell stimulation. However, mIkappaB beta completely blocks NF-kappaB activity after IkappaB alpha degradation. In addition, as a consequence of this inhibition, ikba expression is down regulated, along with that of other NF-kappaB-regulated genes. These transgenic mice have a significant reduction in the peripheral T -cell population, especially CD8+ cells. The remaining T cells have impaired proliferation in response to phorbol 12-myristate 13-acetate plus phytohemagglutinin or calcium ionophore but not to anti-CD3/anti-CD28 costimulation. As a result of these alterations, transgenic animals present defects in immune responses such as delayed-type hypersensitivity and the generation of specific antibodies against T-cell -dependent antigens. These results show that in nonstimulated T cells, IkappaB beta cannot efficiently displace IkappaB alpha bound to RelA-containing complexes and that persistent NF-kappaB activity is required for proper T-cell responses in vivo.

L14 ANSWER 37 OF 39 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1997383944 EMBASE <<LOGINID::20090630>>
TITLE: Ubiquitin-dependent internalization and downregulation of plasma membrane proteins.
AUTHOR: Hicke, Linda (correspondence)
CORPORATE SOURCE: Department of Biochemistry, Northwestern University, 2153 Sheridan Rd, Evanston, IL 60208-3500, United States.
AUTHOR: Hicke, Linda (correspondence)
CORPORATE SOURCE: Department of Biochem., Molec. Biol., Northwestern University, 2153 Sheridan Rd., Evanston, IL 60208-3500, United States.
SOURCE: FASEB Journal, (1997) Vol. 11, No. 14, pp. 1215-1226.
Refs: 90
ISSN: 0892-6638 CODEN: FAJOEC

COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
004 Microbiology: Bacteriology, Mycology, Parasitology and Virology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Jan 1998
Last Updated on STN: 15 Jan 1998

AB The modification of cytosolic proteins with polyubiquitin chains targets them for recognition and degradation by the multisubunit proteolytic particle, the 26S proteasome. Membrane proteins are also substrates for ubiquitination. Integral membrane proteins of the endoplasmic reticulum are ubiquitinated and destroyed by the proteasome (reviewed in refs 1, 2). However, it has been shown recently that the ubiquitination of Saccharomyces cerevisiae plasma membrane proteins signals their degradation by the proteolytic system in the lysosome-like vacuole. Ubiquitination of several different classes of cell surface proteins serves as a signal for their entry into the endocytic pathway; this leads to their transport to the vacuole, where they are permanently inactivated by degradation. In yeast, ubiquitin has been 'unplicated as an internalization signal for most, if not all, endogenous plasma membrane proteins that are known to be endocytosed. Ubiquitin-dependent internalization has been best characterized for two proteins: the mating pheromone α-factor receptor and the uracil permease. Some mammalian cell surface receptors are also ubiquitinated at the plasma membrane. Ubiquitination machinery is required for ligand-induced endocytosis of the growth hormone receptor, suggesting that ubiquitin-dependent endocytosis and sorting is also an important regulatory process in mammalian cells. Mammalian receptors may also be down-regulated through the degradation of their cytosolic domains by a proteasome-dependent pathway.

L14 ANSWER 38 OF 39 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 1996189089 MEDLINE <<LOGINID::20090630>>
DOCUMENT NUMBER: PubMed ID: 8628274
TITLE: Inactivation of IkappaBbeta by the tax protein of human T-cell leukemia virus type 1: a potential mechanism for constitutive induction of NF-kappaB.
AUTHOR: McKinsey T A; Brockman J A; Scherer D C; Al-Murrani S W; Green P L; Ballard D W
CORPORATE SOURCE: Howard Hughes Medical Institute, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.
CONTRACT NUMBER: CA5958-01 (United States NCI NIH HHS)
R01 AI33839 (United States NIAID NIH HHS)
SOURCE: Molecular and cellular biology, (1996 May) Vol. 16, No. 5, pp. 2083-90.
Journal code: 8109087. ISSN: 0270-7306.
Report No.: NLM-PMC231195.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 8 Jul 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 21 Jun 1996

AB In resting T lymphocytes, the transcription factor NF-kappaB is sequestered in the cytoplasm via interactions with members of the I kappa B family of inhibitors, including IkappaBalpha and IkappaBbeta. During

normal T-cell activation, IkappaBalpha is rapidly phosphorylated, ubiquitinated, and degraded by the 26S proteasome, thus permitting the release of functional NF-kappaB. In contrast to its transient pattern of nuclear induction during an immune response, NF-kappaB is constitutively activated in cells expressing the Tax transforming protein of human T-cell leukemia virus type I (HTLV-1). Recent studies indicate that HTLV-1 Tax targets IkappaBalpha to the ubiquitin-proteasome pathway. However, it remains unclear how this viral protein induces a persistent rather than transient NF-kappaB response. In this report, we provide evidence that in addition to acting on IkappaBalpha, Tax stimulates the turnover Of IkappaBbeta via a related targeting mechanism. Like IkappaBalpha, Tax-mediated breakdown of IkappaBbeta in transfected T lymphocytes is blocked either by cell-permeable proteasome inhibitors or by mutation Of IkappaBbeta at two serine residues present within its N-terminal region. Despite the dual specificity of HTLV-1 Tax for IkappaBalpha and IkappaBbeta at the protein level, Tax selectively stimulates NF-kappaB-directed transcription of the IkappaBalpha gene. Consequently, IkappaBbeta protein expression is chronically downregulated in HTLV-1-infected T lymphocytes. These findings with IkappaBbeta provide a potential mechanism for the constitutive activation of NF-kappaB in Tax-expressing cells.

L14 ANSWER 39 OF 39 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 1994019774 MEDLINE <<LOGINID::20090630>>
DOCUMENT NUMBER: PubMed ID: 8413590
TITLE: Valosin-containing protein, VCP, is a ubiquitous clathrin-binding protein.
AUTHOR: Pleasure I T; Black M M; Keen J H
CORPORATE SOURCE: Department of Pharmacology, Thomas Jefferson University, Philadelphia, Pennsylvania 19107.
SOURCE: Nature, (1993 Sep 30) Vol. 365, No. 6445, pp. 459-62. Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 3 Mar 2000
Entered Medline: 1 Nov 1993

AB Clathrin is the structural protein of coated membranes involved in receptor-mediated endocytosis and aspects of Golgi sorting in eukaryotic cells. We have now detected a stoichiometric complex of clathrin with a novel protein of M(r) approximately 100,000 (100K) in lysates of different mammalian cells. Formation of the complex, which also includes the 70K heat-shock protein Hsc70, occurs within 15 min of synthesis. The 100K protein has been identified as valosin-containing protein (VCP; reference 1), an early substrate for tyrosine phosphorylation on T-cell receptor activation. Further, VCP is the mammalian homologue of yeast Cdc48p (reference 3) and is a member of a larger gene family that includes putative ATP-binding proteins involved in vesicle transport and fusion, 26S proteasome function, regulation of the expression of human immunodeficiency virus, and assembly of peroxisomes. The association with clathrin and the morphological and catalytic similarity to the chaperonin proteins indicate that VCP may modulate protein-protein interactions in membrane transport processes.

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NEWS	4	APR 07	STN is raising the limits on saved answers
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NEWS	6	APR 26	USPATFULL and USPAT2 enhanced with patent assignment/reassignment information
NEWS	7	APR 28	CAS patent authority coverage expanded
NEWS	8	APR 28	ENCOMPLIT/ENCOMPLIT2 search fields enhanced
NEWS	9	APR 28	Limits doubled for structure searching in CAS REGISTRY
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NEWS	13	MAY 14	DGENE, PCTGEN and USGENE enhanced with increased limits for exact sequence match searches and introduction of free HIT display format
NEWS	14	MAY 15	INPADOCDB and INPAFAMDB enhanced with Chinese legal status data
NEWS	15	MAY 28	CAS databases on STN enhanced with NANO super role in records back to 1992
NEWS	16	JUN 01	CAS REGISTRY Source of Registration (SR) searching enhanced on STN
NEWS	17	JUN 26	NUTRACEUT and PHARMAML no longer updated
NEWS	18	JUN 29	IMSCOPROFILE now reloaded monthly
NEWS	19	JUN 29	EPFULL adds SLART to AB, MCLM, and TI fields
NEWS EXPRESS		MAY 26	09 CURRENT WINDOWS VERSION IS V8.4, AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2009.
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FILE 'HOME' ENTERED AT 09:46:37 ON 01 JUL 2009

=> file medline scisearch embase
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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=> s melanA
L1          279 MELANA

=> s 27-35
L2         1633 27-35

=> s l1 and l2
L3            8 L1 AND L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4             4 DUP REM L3 (4 DUPLICATES REMOVED)

=> d ibib abs 1-4

L4   ANSWER 1 OF 4  SCISEARCH  COPYRIGHT (c) 2009 The Thomson Corporation  on
     STN
ACCESSION NUMBER:    2009:56865  SCISEARCH <<LOGINID::20090701>>
THE GENUINE ARTICLE: 386NR
TITLE:               Validation of a HLA-A2 tetramer flow cytometric method,
                     IFNgamma real time RT-PCR, and IFNgamma ELISPOT for
                     detection of immunologic response to gp100 and
                     MelanA/MART-1 in melanoma patients
AUTHOR:              Xu, Yuanxin (Reprint)
CORPORATE SOURCE:    Genzyme Corp, 1 Mt Rd, Framingham, MA 01701 USA (Reprint)
                     E-mail: yuanxin.xu@genzyme.com
AUTHOR:              Xu, Yuanxin (Reprint); Theobald, Valerie; Sung, Crystal;
                     DePalma, Kathleen; Atwater, Laura; Seiger, Keirsten;
                     Perricone, Michael A.; Richards, Susan M.
CORPORATE SOURCE:    Genzyme Corp, Framingham, MA 01701 USA
                     E-mail: yuanxin.xu@genzyme.com;
                     valerie.theobald@genzyme.com; crystal.sung@genzyme.com;
                     whaka01@yahoo.com; laura.atwater@genzyme.com;
                     kseiger@comcast.net; michael.perricone@genzyme.com;
                     susan.richards@genzyme.com
COUNTRY OF AUTHOR:   USA
SOURCE:              JOURNAL OF TRANSLATIONAL MEDICINE, (22 OCT 2008) Vol. 6,
                     arn. 61.
                     ISSN: 1479-5876.
PUBLISHER:           BIOMED CENTRAL LTD, CURRENT SCIENCE GROUP, MIDDLESEX
                     HOUSE, 34-42 CLEVELAND ST, LONDON W1T 4LB, ENGLAND.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
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REFERENCE COUNT: 22
ENTRY DATE: Entered STN: 15 Jan 2009
Last Updated on STN: 15 Jan 2009
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: HLA-A2 tetramer flow cytometry, IFN gamma real time RT-PCR and IFN gamma ELISPOT assays are commonly used as surrogate immunological endpoints for cancer immunotherapy. While these are often used as research assays to assess patient's immunologic response, assay validation is necessary to ensure reliable and reproducible results and enable more accurate data interpretation. Here we describe a rigorous validation approach for each of these assays prior to their use for clinical sample analysis.

Methods: Standard operating procedures for each assay were established. HLA-A2 (A*0201) tetramer assay specific for gp100(209(210M)) and MART-1(26-35(27L)), IFN gamma real time RT-PCR and ELISPOT methods were validated using tumor infiltrating lymphocyte cell lines (TIL) isolated from HLA-A2 melanoma patients. TIL cells, specific for gp100 (TIL 1520) or MART-1 (TIL 1143 and TIL1235), were used alone or spiked into cryopreserved HLA-A2 PBMC from healthy subjects. TIL/PBMC were stimulated with peptides (gp100(209), gp100(pool), MART-1(27-35), or influenza-M1 and negative control peptide HIV) to further assess assay performance characteristics for real time RTPCR and ELISPOT methods. Validation parameters included specificity, accuracy, precision, linearity of dilution, limit of detection (LOD) and limit of quantification (LOQ). In addition, distribution was established in normal HLA-A2 PBMC samples. Reference ranges for assay controls were established.

Results: The validation process demonstrated that the HLA-A2 tetramer, IFN gamma real time RT-PCR, and IFN gamma ELISPOT were highly specific for each antigen, with minimal cross-reactivity between gp100 and MelanA/MART-1. The assays were sensitive; detection could be achieved at as few as 1/4545-1/6667 cells by tetramer analysis, 1/50,000 cells by real time RT-PCR, and 1/10,000-1/20,000 by ELISPOT. The assays met criteria for precision with % CV < 20% (except ELISPOT using high PBMC numbers with % CV < 25%) although flow cytometric assays and cell based functional assays are known to have high assay variability. Most importantly, assays were demonstrated to be effective for their intended use. A positive IFN gamma response (by RT-PCR and ELISPOT) to gp100 was demonstrated in PBMC from 3 melanoma patients. Another patient showed a positive MART-1 response measured by all 3 validated methods.

Conclusion: Our results demonstrated the tetramer flow cytometry assay, IFN gamma real-time RTPCR, and INF gamma ELISPOT met validation criteria. Validation approaches provide a guide for others in the field to validate these and other similar assays for assessment of patient T cell response. These methods can be applied not only to cancer vaccines but to other therapeutic proteins as part of immunogenicity and safety analyses.

L4 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003008601 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 12491520
TITLE: Granulocyte-macrophage-colony-stimulating factor added to a multipeptide vaccine for resected Stage II melanoma.
AUTHOR: Weber Jeffrey; Sondak Vernon K; Scotland Ronaldo; Phillip Ramila; Wang Flora; Rubio Valerie; Stuge Tor B; Groshen Susan G; Gee Conway; Jeffery Georgia G; Sian Shirley; Lee Peter P
CORPORATE SOURCE: Department of Medicine, Division of Medical Oncology, Keck/University of Southern California School of Medicine, Los Angeles, CA, USA.. jweber@hsc.usc.edu
CONTRACT NUMBER: 5P30 CA 14089 (United States NCI NIH HHS)

R01 CA 090809 (United States NCI NIH HHS)
SOURCE: Cancer, (2003 Jan 1) Vol. 97, No. 1, pp. 186-200.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 8 Jan 2003
Last Updated on STN: 25 Jan 2003
Entered Medline: 24 Jan 2003

AB BACKGROUND: Forty-eight patients with resected Stages IIA and IIB melanoma were immunized with two tumor antigen epitope peptides derived from gp100(209-217) (210M) (IMDQVPSFV) and tyrosinase(368-376) (370D) (YMDGTMSQV) emulsified with incomplete Freund's adjuvant (IFA). Patients were assigned randomly to receive either peptides/IFA alone or with 250 microm of granulocyte-macrophage-colony-stimulating factor (GM-CSF) subcutaneously daily for 5 days to evaluate the toxicities and immune responses in either arm. Time to recurrence and survival were secondary end points. METHODS: Immunizations were administered every 2 weeks x 4, then every 4 weeks x 3, and once 8 weeks later. A leukapheresis to obtain peripheral blood mononuclear cells for immune analyses and skin testing with peptides and recall reagents was performed before and after eight vaccinations. RESULTS: Local pain and granuloma formation, fever, and lethargy of Grade 1 or 2 were observed. Transient vaccine-related Grade III and no Grade IV toxicity was observed. Seventeen of the 40 patients for whom posttreatment skin tests were performed developed a positive skin test response to the gp100 peptide, but only 1 of the 40 patients developed a positive skin test response to tyrosinase. Immune responses were measured by release of interferon-gamma (IFN-gamma) in an enzyme-linked immunosorbent assay (ELISA) by effector cells in the presence of peptide-pulsed antigen-presenting cells, by cytokine release of IFN-gamma, GM-CSF, and tumor necrosis factor-alpha in a Luminex assay, or by an antigen-specific tetramer flow cytometry assay. Thirty-four of the 39 patients for whom the ELISA data were performed demonstrated an immune response after vaccination, as did 37 of 42 patients by tetramer assay. Enzyme-linked immunosorbent assay, Luminex, and tetramer responses in the GM-CSF/peptide/IFA group were higher than in the peptide/IFA group. Epitope spreading to the MART-1/MelanA 27-35
and 26-35 (27L) epitopes was detected by tetramer assay in 10 patients. Seven of 48 patients experienced disease recurrence with a median of 24 months of follow-up and 2 patients in this intermediate to high risk group have died. CONCLUSION: These data suggest a significant number of patients with resected melanoma mount an antigen-specific immune response against a peptide vaccine. There is a trend for GM-CSF to modestly increase the immune response and support further development of GM-CSF as a vaccine adjuvant.

L4 ANSWER 3 OF 4 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:198231 SCISEARCH <<LOGINID::20090701>>
THE GENUINE ARTICLE: 175QB
TITLE: Assessment of immunogenicity of human melan-A peptide analogues in HLA-A*0201/K-b transgenic mice
AUTHOR: Miconnet I (Reprint)

CORPORATE SOURCE: Univ Lausanne, Ludwig Inst Canc Res, Lausanne Branch, Chemin Boveresses 155, CH-1066 Epalinges, Switzerland (Reprint)
AUTHOR: Men Y; Valmori D; Rimoldi D; Cerottini J C; Romero P
CORPORATE SOURCE: Univ Lausanne, Ludwig Inst Canc Res, Lausanne Branch, CH-1066 Epalinges, Switzerland; CHU Vaudois, Ludwig Inst Canc Res, Lausanne Branch, Div Clin Oncoimmunol, CH-1011 Lausanne, Switzerland
COUNTRY OF AUTHOR: Switzerland
SOURCE: JOURNAL OF IMMUNOLOGY, (15 MAR 1999) Vol. 162, No. 6, pp. 3566-3573.
ISSN: 0022-1767.
PUBLISHER: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 56
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Previous studies have shown that substitution of single amino acid residues in human Melan-A immunodominant peptides MelanA(27-35) and Melan-A(26-35) greatly improved their binding and the stability of peptide/HLA-A*0201 complexes. In particular, one Melan-A peptide analogue was more efficient in the generation of Melan-A peptide-specific and melanoma-reactive CTL than its parental peptide in vitro from human PDL. In this study, we analyzed the in vivo immunogenicity of Melan-A natural peptides and their analogues in HLA-A*0201/K-b transgenic mice. We found that two human Melan-A natural peptides, Melan-A(26-35) and Melan-A(27-35), were relatively weak immunogens, whereas several Melan-A peptide analogues were potent immunogens for in vivo CTL priming. In addition, induced Melan-A peptide-specific mouse CTL cross-recognized natural Melan-A peptides and their analogues. More interestingly, these mouse CTL were also able to lyse human melanoma cell lines in vitro in a HLA-A*0201-restricted, Melan-A-specific manner. Our results indicate that the HLA-A*0201/K-b transgenic mouse is a useful animal model to perform preclinical testing of potential cancer vaccines, and that Melan-A peptide analogues are attractive candidates for melanoma immunotherapy.

L4 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 1997031815 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 8877721
TITLE: Differential anti-MART-1/MelanA CTL activity in peripheral blood of HLA-A2 melanoma patients in comparison to healthy donors: evidence of in vivo priming by tumor cells.
AUTHOR: Marincola F M; Rivoltini L; Salgaller M L; Player M; Rosenberg S A
CORPORATE SOURCE: Surgery Branch, National Cancer Institute, Bethesda, MD 20892-1502, USA.
SOURCE: Journal of immunotherapy with emphasis on tumor immunology : official journal of the Society for Biological Therapy, (1996 Jul) Vol. 19, No. 4, pp. 266-77.
Journal code: 9418950. ISSN: 1067-5582.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702

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ENTRY DATE:          Entered STN: 19 Feb 1997
                     Last Updated on STN: 19 Feb 1997
                     Entered Medline: 4 Feb 1997
AB   MART-1 is expressed ir both normal and neoplastic cells of melanocytic
     origin.  Peripheral blood mononuclear cells (PBMC) from melanoma patients
     recognize and lyse tumor cells after repetitive in vitro stimulation with
     the immunodominant peptide MART-1(27-35).  In this
     study, we compared the characteristics of the cytotoxic T lymphocyte (CTL)
     response to MART-1 in PBMC from 13 HLA-A2 melanoma patients with PBMC from
     9 normal healthy donors stimulated in vitro with MART-1(27-
     35) (AAGIGILTV) or FluM1(58-66) (GILGFVFTL) peptides.  The
     expansion rate among CTLs from different patients was variable and did not
     correlate with the development of specificity against the MART-1(
     27-35) or FluM1(58-66) peptides.  Specific anti-MART-1(
     27-35) cytotoxicity could be generated in 13 of 13
     melanoma patients but only in 5 of 9 healthy donors (p < 0.001).
     Anti-FluM1(58-66) activity could be generated in six of seven melanoma
     patients and six of seven healthy donors.  Specific activity against
     MART-1(27-35), but not FluM1(58-66), was detectable
     significantly earlier after repetitive in vitro stimulation in melanoma
     patients (22.7 +/- 2.0 days compared with 32.7 +/- 1.7 days for healthy
     donors, p < 0.01).  This report provides the first evidence of an enhanced
     level of sensitization of tumor-bearing hosts compared with normal
     individuals against a differentiation antigen shared by tumor and normal
     cells of the same lineage.  These findings may have important implications
     for delineating events involved in the biology of tumor rejection
     naturally or in response to active specific immunotherapy.


=> s melanA or mart-1 or AAGIGILTV
L5        2098 MELANA OR MART-1 OR AAGIGILTV

=> s t()cell or t()lymphocyte
=> s t()cell or t()lymphocyte
L6      632226 T(W) CELL OR T(W) LYMPHOCYTE

=> s l5 and l6
L7         945 L5 AND L6

=> s l7 and adoptive
L8         114 L7 AND ADOPTIVE

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9           70 DUP REM L8 (44 DUPLICATES REMOVED)

=> s l9 not py>2000
L10         24 L9 NOT PY>2000

=> d ibib abs 1-24

L10  ANSWER 1 OF 24     MEDLINE on STN
ACCESSION NUMBER:   2007695528     IN-PROCESS <<LOGINID::20090701>>
DOCUMENT NUMBER:    PubMed ID: 18031135
TITLE:              Cancer immunotherapy: is there real progress at last?.
AUTHOR:             Kammula U S; Marincola F M
CORPORATE SOURCE:   Surgery Branch, Division of Clinical Sciences, National
                    Institutes of Health, Bethesda, Maryland, USA.
SOURCE:             BioDrugs : clinical immunotherapeutics, biopharmaceuticals
                    and gene therapy, (1999 Apr) Vol. 11, No. 4, pp. 249-60.
                    Journal code: 9705305. ISSN: 1173-8804.
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PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED
ENTRY DATE: Entered STN: 24 Nov 2007
Last Updated on STN: 10 Dec 2007

AB This review summarises the evolution of recent major advances in cancer immunotherapy, using metastatic melanoma as a model. The first true clinical progress with immunotherapy developed from the application of recombinant DNA technology for the large scale production of immunostimulant cytokines. Clinical trials demonstrated that the systemic administration of recombinant high-dose bolus intravenous interleukin-2 (IL-2; 720 000 IU/kg every 8 hours) mediated objective tumour progression in 20% of patients with metastatic renal cancer and in 17% of patients with metastatic melanoma, with complete responses of 9% and 7%, respectively. The use of adoptive immunotherapy (the transfer of immune cells with anti-tumour activity to the tumour-bearing host) focused interest on T lymphocyte-mediated tumour recognition. Clinical trials described the systemic administration of lymphokine activated killer (LAK) cells and subsequently tumour infiltrating lymphocytes (TIL) to patients with advanced cancer. Although able to kill tumour targets in vitro, LAK cells did not prove useful for the treatment of patients with metastatic melanoma and renal cancer. A randomised trial, in which IL-2 was administered alone or with LAK cells, failed to show a difference in response rate or survival. In contrast, the treatment of 86 patients with metastatic melanoma using TIL plus IL-2 resulted in a 34% objective response rate, which included patients who had previously failed treatment with high-dose IL-2 alone. The focus on cellular immune responses, combined with rapid biotechnological advances, resulted in the identification of tumour specific antigens, such as MART-1 and gp100, that could be recognised by autologous TIL. This provided fundamental evidence of the existence of melanoma-associated antigens that were recognised in vivo by effector cells of the immune system. In vitro studies demonstrated immunodominant epitopes from MART-1 and gp100 that could induce in vitro-specific cytotoxic T lymphocyte reactivity. To enhance in vitro immunogenicity, single amino acid substitutions were made to identify peptides with higher affinity for HLA-A*0201. Modified peptides from gp100 were compared with the parental peptide for increased immunogenicity based on their ability to induce anti-tumour lymphocytes in vitro. From these studies, a candidate peptide was identified (G9-209-2M) which had increased immunogenic reactivity in vitro. Clinical trials demonstrated that the modified G9-209-2M peptide was more effective. Unfortunately, objective tumour regression was still low. However, when high-dose IL-2 was combined with G9-209-2M objective clinical responses increased to 42%. Efforts to find better ways to immunise against self antigens are ongoing and involve further peptide immunisations, as well as recombinant viral vectors, adjuvant cytokine therapy and cellular adjuvants such as dendritic cells.

L10 ANSWER 2 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2001091662 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 11104805
TITLE: Melanocyte destruction after antigen-specific immunotherapy of melanoma: direct evidence of t cell -mediated vitiligo.
AUTHOR: Yee C; Thompson J A; Roche P; Byrd D R; Lee P P; Piepkorn M; Kenyon K; Davis M M; Riddell S R; Greenberg P D
CORPORATE SOURCE: Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.
CONTRACT NUMBER: R01 CA71849 (United States NCI NIH HHS)

SOURCE: The Journal of experimental medicine, (2000 Dec 4) Vol. 192, No. 11, pp. 1637-44.
Journal code: 2985109R. ISSN: 0022-1007.
Report No.: NLM-PMC2193107.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 25 Jan 2001

AB Current strategies for the immunotherapy of melanoma include augmentation of the immune response to tumor antigens represented by melanosomal proteins such as tyrosinase, gp100, and MART-1. The possibility that intentional targeting of tumor antigens representing normal proteins can result in autoimmune toxicity has been postulated but never demonstrated previously in humans. In this study, we describe a patient with metastatic melanoma who developed inflammatory lesions circumscribing pigmented areas of skin after an infusion of MART -1-specific CD8(+) T cell clones. Analysis of the infiltrating lymphocytes in skin and tumor biopsies using T cell-specific peptide-major histocompatibility complex tetramers demonstrated a localized predominance of MART-1 -specific CD8(+) T cells (>28% of all CD8 T cells) that was identical to the infused clones (as confirmed by sequencing of the complementarity-determining region 3). In contrast to skin biopsies obtained from the patient before T cell infusion, postinfusion biopsies demonstrated loss of MART-1 expression, evidence of melanocyte damage, and the complete absence of melanocytes in affected regions of the skin. This study provides, for the first time, direct evidence in humans that antigen-specific immunotherapy can target not only antigen-positive tumor cells in vivo but also normal tissues expressing the shared tumor antigen.

L10 ANSWER 3 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2001058362 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 10916759
TITLE: Phase 1 study in patients with metastatic melanoma of immunization with dendritic cells presenting epitopes derived from the melanoma-associated antigens MART -1 and gp100.
AUTHOR: Panelli M C; Wunderlich J; Jeffries J; Wang E; Mixon A; Rosenberg S A; Marincola F M
CORPORATE SOURCE: Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892-1502, USA.
SOURCE: Journal of immunotherapy (Hagerstown, Md. : 1997), (2000 Jul-Aug) Vol. 23, No. 4, pp. 487-98.
Journal code: 9706083. ISSN: 1524-9557.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001

Entered Medline: 22 Dec 2000

AB Dendritic cells (DCs) have been shown to enhance anti-tumor immune responses in several preclinical models. Furthermore, DC-like function can be elicited from peripheral blood monocytes cultured in vitro with interleukin-4 and granulocyte-macrophage colony-stimulating factor. For this reason, a phase 1 study was initiated at the Surgery Branch of the National Cancer Institute to test the toxicity and biological activity of the intravenous administration of peripheral blood monocyte-derived DCs. The DCs were generated by 5- to 7-day incubation in interleukin-4 (1,000 U/mL) and granulocyte-macrophage colony-stimulating factor (1,000 U/mL) of peripheral blood monocytes obtained by leukapheresis. Before administration, the DCs were pulsed separately with the HLA-A*0201-associated melanoma epitopes MART-1(27-35) and gp-100-209-2M. The DCs were administered four times at 3-week intervals. A first cohort of patients (n = 3) was treated with 6 x 10(7) DCs and a second cohort (n = 5) with 2 x 10(8) DCs (in either case, one half of the DCs were pulsed with MART-1(27-35) and the other half was pulsed with gp-100-209-2M). In a final cohort under accrual (n = 2) 2 x 10(8) DCs were administered in combination with interleukin-2 (720,000 IU/kg every 8 hours). The recovery of DCs after in vitro culture ranged from 3% to 35% (mean, 15%) of the original peripheral blood monocytes. Administration of DCs caused no symptoms at any of the doses, and the concomitant administration of interleukin-2 did not cause toxicity other than that expected for interleukin-2 alone. Monitoring of patients' cytotoxic T lymphocyte reactivity before and after treatment revealed enhancement of cytotoxic T lymphocyte reactivity only in one of five patients tested. Of seven patients evaluated for response, one had a transient partial response with regression of pulmonary and cutaneous metastases. A relatively large number of DCs can be safely administered intravenously. The poor clinical outcome of this study perhaps could be explained by the type of protocol used for DC maturation, the route of administration, or both. For this reason, this clinical protocol was interrupted prematurely, whereas other strategies for DC preparation and route of administration are being investigated at the authors' institution.

L10 ANSWER 4 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2001035897 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 11033019
TITLE: Identification of HLA-A*03, A*11 and B*07-restricted melanoma-associated peptides that are immunogenic in vivo by vaccine-induced immune response (VIIR) analysis.
AUTHOR: Reynolds S R; Celis E; Sette A; Oratz R; Shapiro R L; Johnston D; Fotino M; Bystryn J C
CORPORATE SOURCE: The Ronald O. Perelman Department of Dermatology, New York University Medical Center, New York, NY 10016, USA.. srr3@is.nyu.edu
CONTRACT NUMBER: P30CA16087 (United States NCI NIH HHS)
R01AM27663-09 (United States NIADDK NIH HHS)
R21CA78659 (United States NCI NIH HHS)
+
SOURCE: Journal of immunological methods, (2000 Oct 20) Vol. 244, No. 1-2, pp. 59-67.
Journal code: 1305440. ISSN: 0022-1759.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011

ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 30 Nov 2000

AB With the discovery of increasing numbers of tumor antigens, there is a need to rapidly determine whether these antigens and the individual peptides they express are able to stimulate immune responses in vivo and thus, can be used to construct cancer vaccines. In this study we used the method of vaccine-induced immune response (VIIR) analysis to identify multiple immunogenic peptide epitopes derived from several melanoma associated antigens and presented by HLA-A*03, A*11 and B*07. Thirty-one patients with melanoma were immunized to a polyvalent vaccine containing multiple antigens, including MAGE-3, Melan A/MART-1, gp100 and tyrosinase. Their peripheral blood was tested for peptide-specific, vaccine-induced CD8+ T cell responses before and after immunization using an enzyme-linked immune spot (ELISPOT) assay with panels of peptides restricted by these three alleles. The peptides were selected for immunogenic potential based on their strong binding affinity in vitro to HLA-A*03, A*11 or B*07. Overall, 60% of the 20 peptides studied were recognized by at least one patient and 50% of the patients showed a vaccine-induced CD8+ T cell response to at least one peptide that matched their HLA specificity. We conclude that VIIR analysis is an effective strategy to directly identify immunogenic peptides that are good candidates for vaccine construction.

L10 ANSWER 5 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2000290311 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 10832714
TITLE: New cancer therapy by immunomanipulation: development of immunotherapy for human melanoma as a model system.
AUTHOR: Kawakami Y
CORPORATE SOURCE: Division of Cellular Signaling, Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, Japan.. yutakawa@med.keio.ac.jp
SOURCE: Cornea, (2000 May) Vol. 19, No. 3 Suppl, pp. S2-6. Ref: 27
Journal code: 8216186. ISSN: 0277-3740.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 11 Aug 2000
Last Updated on STN: 11 Aug 2000
Entered Medline: 31 Jul 2000

AB PURPOSE AND METHODS: T cells play an important role in in vivo rejection of human melanoma. Human melanoma antigens recognized by autologous T cells were identified. These antigens are classified as tissue (melanocyte)-specific proteins, cancer-testis antigens (proteins expressed in normal testis and various cancers), tumor-specific peptides derived from mutations in tumor cells, and others. RESULTS: A variety of mechanisms generating T cell epitopes on tumor cells were discovered. Various clinical observations, including tumor regression observed in adoptive transfer of gp100-reactive T cells suggest that these identified melanoma peptides may function as tumor rejection antigens. Immunodominant common epitopes that could expand melanoma-reactive cytotoxic T lymphocytes (CTLs) in vitro were found in the MART-1 and gp100 antigens. New immunization protocols--including immunization with peptides, recombinant viruses, plasmid DNAs, and dendritic cells pulsed with peptides as well as adoptive transfer of in vitro-generated CTLs by stimulation with antigenic peptides--were developed (phase I clinical trials have been

performed in the Surgery Branch of the National Cancer Institute, Bethesda, MD, U.S.A.). Immunization with the gp100(209(210M)) peptide that was modified to have high HLA-A2 binding affinity, along with incomplete Freund's adjuvant and interleukin (IL)-2, resulted in a 42% response rate in patients with melanoma. CONCLUSION: These immunotherapies need further improvement due to the mechanisms of tumor escape from T cell responses.

L10 ANSWER 6 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2000151766 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 10687150
TITLE: Dendritic cells loaded with MART-1 peptide or infected with adenoviral construct are functionally equivalent in the induction of tumor-specific cytotoxic T lymphocyte responses in patients with melanoma.
AUTHOR: Philip R; Alters S E; Brunette E; Ashton J; Gadea J; Yau J; Lebkowski J; Philip M
CORPORATE SOURCE: RPR Gencell, Hayward, California, USA.
SOURCE: Journal of immunotherapy (Hagerstown, Md. : 1997), (2000 Jan) Vol. 23, No. 1, pp. 168-76.
Journal code: 9706083. ISSN: 1524-9557.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 18 May 2000
Last Updated on STN: 18 May 2000
Entered Medline: 11 May 2000
AB Immunization with tumor-specific-associated antigen--pulsed dendritic cells has proved to be efficacious in various animal models and is being evaluated for the treatment of cancer in humans. Use of dendritic cells pulsed with specific peptides or transfected with tumor-associated antigen genes has been a focused area of investigation for inducing potent tumor and viral immune responses. In this study, the authors demonstrate transgene expression, including the lacZ and MART-1 genes, in dendritic cells infected with adenoviral constructs. These transiently transduced dendritic cells, derived from melanoma patients' monocytes cultured with granulocyte-macrophage colony-stimulating factor and interleukin-4, express the transgene and can stimulate patients' CD8+ T cells to elicit an antitumor immune response comparable to dendritic cells loaded with a defined peptide. These cytotoxic T lymphocytes were able to recognize both known and unknown tumor-associated antigen epitopes and exhibited cytolytic activity against HLA-matched tumor cells expressing the antigen. The ability to induce tumor-specific cytotoxic T lymphocytes in vitro using gene-modified dendritic cells that transiently express tumor-associated antigens demonstrates the potential use of these antigen-presenting cells for developing in vivo cancer vaccines.

L10 ANSWER 7 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2000151750 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 10687134
TITLE: Recognition of shared melanoma antigens in association with major HLA-A alleles by tumor infiltrating T lymphocytes from 123 patients with melanoma.
AUTHOR: Kawakami Y; Dang N; Wang X; Tupesis J; Robbins P F; Wang R F; Wunderlich J R; Yannelli J R; Rosenberg S A
CORPORATE SOURCE: Surgery Branch, National Cancer Institutes, National Institutes of Health, Bethesda, Maryland 20892, USA.
SOURCE: Journal of immunotherapy (Hagerstown, Md. : 1997), (2000

Jan) Vol. 23, No. 1, pp. 17-27.
Journal code: 9706083. ISSN: 1524-9557.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 18 May 2000
Last Updated on STN: 18 May 2000
Entered Medline: 11 May 2000

AB A total of 123 tumor-infiltrating T lymphocyte (TIL) cultures established from patients with HLA-A1, -A2, -A3, -A24, or -A31 metastatic melanoma in the Surgery Branch, National Cancer Institute, were screened for recognition of shared melanoma antigens including five melanosomal proteins (tyrosinase, MART-1/melan-A, gp100, TRP1, TRP2) as well as peptides derived from MAGE-1 and MAGE-3. Examination of the specificity of these T cells indicated that 16% of HLA-A1 TIL, 57% of HLA-A2 TIL, 7% of HLA-A3 TIL, 13% of HLA-A24 TIL, and 27% of HLA-A31 TIL recognized shared melanoma antigens restricted by major histocompatibility complex class I. Melanosomal proteins were frequently recognized by these TIL, and MART-1(27-35), gp100(154-162), gp100(209-217), and gp100(280-288) represent highly immunogenic epitopes that were recognized by a high percentage of HLA-A2 restricted melanoma reactive TIL. Recognition of gp100 by HLA-A2 restricted TIL significantly correlated with clinical response to adoptive immunotherapy with TIL in 21 HLA-A2 melanoma patients (p = 0.024). Four HLA-A1, two HLA-A2, two HLA-A3, one HLA-A24, and two HLA-A31 restricted shared antigen-specific TIL did not recognize the previously identified antigens tested in this study, and may be useful for the identification of new melanoma antigens. The observation that TILs isolated from patients with metastatic melanoma recognized melanosomal proteins in the context of predominant HLA-A alleles implies that it may be possible to develop immunotherapies for patients with melanoma expressing diverse HLA types.

L10 ANSWER 8 OF 24 MEDLINE on STN
ACCESSION NUMBER: 1999049508 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 9833762
TITLE: Circulating Melan-A/Mart-1 specific cytolytic T lymphocyte precursors in HLA-A2+ melanoma patients have a memory phenotype.
AUTHOR: D'Souza S; Rimoldi D; Lienard D; Lejeune F; Cerottini J C; Romero P
CORPORATE SOURCE: Multidisciplinary Oncology Center, CHUV, Lausanne, Switzerland.
SOURCE: International journal of cancer. Journal international du cancer, (1998 Dec 9) Vol. 78, No. 6, pp. 699-706.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 15 Jan 1999
Last Updated on STN: 15 Jan 1999
Entered Medline: 4 Dec 1998

AB Melan-A/MART-1 is a melanoma differentiation antigen that is recognized by a high proportion of cytolytic T lymphocyte (CTL) clones derived from human leukocyte antigen (HLA)-A2+ melanoma patients. Whereas peptide Melan-A/ MART-

1(27-35) was originally defined as the immunodominant CTL epitope, we have previously reported that peptide Melan-A/MART-1 (26-35) was recognized more efficiently by the majority of tumor-reactive CTL clones. As demonstrated here, CTL populations generated from blood lymphocytes of either melanoma patients or healthy individuals after in vitro stimulation with peptide Melan-A/MART-1(26-35) killed specifically HLA-A2+ Melan-A+ allogeneic melanoma cells, thus suggesting their potential use in adoptive immunotherapy. We characterized the surface phenotype of the circulating CTL precursors (CTLp), which respond to in vitro stimulation with peptide Melan-A/MART-1(26-35). In melanoma patients, these CTLp predominantly expressed the CD45RO memory marker. In contrast, they were mainly, although not exclusively, found in the CD45RA subpopulation of CD8 T cells in healthy individuals. The demonstration that Melan-A/MART-1-specific CTLp in peripheral blood lymphocytes from HLA-A2+ patients with metastatic melanoma express a memory phenotype provides direct evidence that in vivo priming of this antigen may occur during tumor progression.

L10 ANSWER 9 OF 24 MEDLINE on STN
ACCESSION NUMBER: 1998336716 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 9672845
TITLE: The use of melanosomal proteins in the immunotherapy of melanoma.
AUTHOR: Kawakami Y; Robbins P F; Wang R F; Parkhurst M; Kang X; Rosenberg S A
CORPORATE SOURCE: Surgery Branch, National Institutes of Health, Bethesda, MD 20892-1502, USA.
SOURCE: Journal of immunotherapy (Hagerstown, Md. : 1997), (1998 Jul) Vol. 21, No. 4, pp. 237-46. Ref: 75
Journal code: 9706083. ISSN: 1524-9557.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 8 Oct 1998
Last Updated on STN: 8 Oct 1998
Entered Medline: 1 Oct 1998

AB Clinical observations in the interleukin (IL) 2-based immunotherapies suggest that T cells play a central role in the rejection of melanoma. Using cDNA expression cloning, we have isolated genes encoding melanoma antigens recognized by tumor-infiltrating T lymphocytes. These antigens are categorized as (a) melanocyte-specific melanosomal proteins (MART-1/melan A, gp100, tyrosinase, TRP-1, and TRP-2), (b) tumor-specific mutated proteins (beta-catenin), and (c) others (p15). A variety of mechanisms has been identified for the generation of T cell epitopes on tumor cells. Some of the HLA-A2 binding epitopes from the melanosomal antigens appear to be subdominant self-determinants with relatively low major histocompatibility complex binding affinity. The effectiveness of adoptive transfer into patients of cytotoxic T lymphocytes recognizing the melanosomal antigens, the significant correlation between vitiligo development and clinical response in patients receiving IL-2-based immunotherapies, and the sporadic tumor regressions observed in some patients following immunization with the MART-1 or gp100 peptides in incomplete Freund's adjuvant or recombinant viruses expressing the MART-1 antigen suggest that these epitopes may represent tumor rejection antigens. Phase I immunization trials using peptides or recombinant viruses containing genes encoding the melanosomal antigens

MART-1 or gp100, with or without co-administration of cytokines such as IL-2, IL-12, or granulocyte-macrophage colony-stimulating factor, are being conducted in the Surgery Branch of the National Cancer Institute. These studies may demonstrate the feasibility of using melanosomal proteins for the immunotherapy of patients with melanoma.

L10 ANSWER 10 OF 24 MEDLINE on STN
ACCESSION NUMBER: 1998053905 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 9393756
TITLE: T-cell receptor repertoire in matched MART-1 peptide-stimulated peripheral blood lymphocytes and tumor-infiltrating lymphocytes.
AUTHOR: Cole D J; Wilson M C; Rivoltini L; Custer M; Nishimura M I
CORPORATE SOURCE: Department of Surgery and Hollings Cancer Center, Medical University of South Carolina, Charleston 29425, USA.
SOURCE: Cancer research, (1997 Dec 1) Vol. 57, No. 23, pp. 5320-7. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 12 Mar 1998 Last Updated on STN: 12 Mar 1998 Entered Medline: 2 Mar 1998

AB Characterization of tumor-associated antigens (TAAs) recognized by CTLs makes the consideration of therapeutic strategies based on peptide stimulation of peripheral blood lymphocytes (PBLs) feasible. Several such approaches are adoptive transfer of peptide-stimulated PBLs, ex vivo peptide stimulation of dendritic cells, and direct vaccination with TAA-derived peptides. A critical component of any of these peptide-based strategies is the requirement that the patient's PBLs are able to react productively against the presented TAA. The purpose of this study, through the study of T-cell receptor (TCR) usage, was to evaluate the T-cell response in matched MART-1(27-35) peptide-stimulated PBLs and tumor-infiltrating lymphocytes (TILs). MART-1 (27-35)-reactive PBL and TIL cultures were generated from three patients by in vitro stimulation with an immunodominant peptide of MART-1 (MART-1(27-35)). All cultures had a human leukocyte antigen A2-restricted, MART-1 (27-35)-specific CTL response. The TCR usage of each was assessed by the DNA sequence analysis of 50 TCR beta clones obtained by rapid amplification of cDNA ends per culture. TCR analysis suggests a TCR repertoire that differed from patient to patient (8-16 subfamilies were used) and a predominant usage of a different variable beta chain (BV) by each of these MART-reactive T cells. These predominant BV rearrangements were derived from multiple clonotypes because different variable, diversity, and junctional regions were observed. However, a similar pattern of expansion was present for both PBLs and TILs; the relative usage of each prevailing BV was more marked in TILs (36, 50, and 78% of TILs versus 26, 20, and 24% of PBLs, respectively), a broader TCR repertoire was used by PBLs ($P > 0.05$), and similar TCR subfamily usage was noted when TIL and PBL cultures from the same patient were compared (8 of 11, 7 of 9, and 7 of 8 for patients 1, 2, and 3, respectively). Furthermore, the exact same clonotypes derived from predominant TCR subfamilies in the PBLs and TILs were present in each patient, suggesting peptide-stimulated expansion in both biological compartments. These studies suggest that there will not be a limited and predictable TCR

subfamily response to a specific TAA, although reproducible patterns of PBL and TIL expansion are present from patient to patient. Additionally, identical T-cell clonotypes having the same potential for antigen-driven expansion were present in a patient's PBLs and TILs. As such, our data support the conceptualization of approaches using adoptive transfer or vaccination based on TAA-derived peptide stimulation of PBLs.

L10 ANSWER 11 OF 24 MEDLINE on STN
ACCESSION NUMBER: 1998021356 MEDLINE <<LOGINID::20090701>>
DOCUMENT NUMBER: PubMed ID: 9378563
TITLE: Generation of Melan-A/MART-1-specific CD8+ cytotoxic T lymphocytes from human naive precursors: helper effect requirement for efficient primary cytotoxic T lymphocyte induction in vitro.
AUTHOR: Ostankovitch M; Le Gal F A; Connan F; Chassin D; Choppin J; Guillet J G
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, Institut Cochin de Genetique Moleculaire, Universite Rene Descartes, Paris, France.. ostankovitch@icgm.cochin.inserm.fr
SOURCE: International journal of cancer. Journal international du cancer, (1997 Sep 17) Vol. 72, No. 6, pp. 987-94. Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 24 Dec 1997
Last Updated on STN: 24 Dec 1997
Entered Medline: 10 Nov 1997
AB This study investigates the generation of primary melanoma cell-specific cytotoxic T lymphocytes (CTLs) in vitro. Induction of peptide-specific CTLs from unfractionated naive peripheral blood mononuclear cells from HLA-A2 healthy donors was assessed using 2 recently described 9-mer epitopes from the melanoma tumor antigen Melan-A/MART-1 . The need for help from CD4+ T lymphocytes for the long-lasting induction of CTLs and the capacity of the peptide-induced CTL lines to recognize many melanoma cells were evaluated. CTL lines were obtained reproducibly when CD4+ T-lymphocyte help was provided during the primary stimulation either in an autologous way, in the case of tetanus toxoid antigen (TT) responder donors, or with allogeneic TT-activated T-helper cells, separated by an insert well, in the case of tetanus toxoid non-responder donors. We also investigated helper T-cell-derived factors that are produced by TT-activated lymphocytes. Our results strongly suggest that a complex network of cytokines like interleukin-2 (IL-2), interferon-gamma, IL-6 and IL-1 exerts stimulatory effects for the initiation process of CTLs. In contrast, cytokine-like IL-4 might inhibit generation of cytolytic activity if provided by TT-activated T cells at early stages of induction. Our approach can be used to generate CTLs of a desired specificity for clinical use in adoptive immunotherapy protocols.

L10 ANSWER 12 OF 24 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:648705 SCISEARCH <<LOGINID::20090701>>
THE GENUINE ARTICLE: 346DZ
TITLE: Synthetic insertion signal sequences enhance MHC class I presentation of a peptide from the melanoma antigen

MART-1
AUTHOR: Minev B R (Reprint)
CORPORATE SOURCE: Univ Calif San Diego, Ctr Canc, Bldg UC303, Room 101, La Jolla, CA 92093 USA (Reprint)
AUTHOR: Chavez F L; Dudouet B M; Mitchell M S
CORPORATE SOURCE: Univ Calif San Diego, Ctr Canc, La Jolla, CA 92093 USA; Univ Calif San Diego, Sch Med, La Jolla, CA 92093 USA; Sidney Kimmel Canc Ctr, San Diego, CA USA; Karmanis Canc Inst, Detroit, MI USA
COUNTRY OF AUTHOR: USA
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (AUG 2000) Vol. 30, No. 8, pp. 2115-2124.
ISSN: 0014-2980.
PUBLISHER: WILEY-V C H VERLAG GMBH, PO BOX 10 11 61, D-69451 BERLIN, GERMANY.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 51
ENTRY DATE: Entered STN: 2000
Last Updated on STN: 2000
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cytotoxic T lymphocytes (CTL) recognize minimal peptides of eight to ten residues which are the products of intracellularly processed proteins and are presented at the cell surface by MHC class I molecules. An important step in this process is the translocation of processed proteins from the cytosol across the endoplasmic reticulum membrane mediated by transporter associated with antigen processing (TAP) proteins, or as an alternative, by endoplasmic reticulum insertion signal sequences. We report here that the addition of synthetic signal sequences at the N terminus, but not at the C terminus, of an epitope from the human melanoma antigen MART-1 greatly enhances its presentation in both TAP-deficient and TAP-expressing cells. A newly designed peptide construct, composed of the epitope replacing the hydrophobic part of a natural signal sequence, was also very effective. Interestingly, an artificial signal sequence containing the same epitope was the most efficient construct for enhancing its presentation. These peptide constructs facilitated epitope presentation when loaded into the cytosol of TAP-deficient T2 cells, TAP-expressing melanoma cells and human dendritic cells. These findings may be of practical significance for the development of synthetic anti-cancer vaccines and in vitro immunization of CTL for adoptive immunotherapy.

L10 ANSWER 13 OF 24 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:198253 SCISEARCH <<LOGINID::20090701>>
THE GENUINE ARTICLE: 175QE
TITLE: Quantitation of T-cell receptor frequencies by competitive PCR: Generation and evaluation of novel TCR subfamily and clone specific competitors
AUTHOR: Nishimura M I (Reprint)
CORPORATE SOURCE: NCI, Surg Branch, NIH, Bldg 10, Rm 2B06, Bethesda, MD 20892 USA (Reprint)
AUTHOR: McKee M D; Clay T M; Rosenberg S A
CORPORATE SOURCE: NCI, Surg Branch, NIH, Bethesda, MD 20892 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF IMMUNOTHERAPY, (MAR 1999) Vol. 22, No. 2, pp. 93-102.
ISSN: 1053-8550.
PUBLISHER: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
DOCUMENT TYPE: Article; Journal

LANGUAGE: English
REFERENCE COUNT: 51
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB T cell receptor (TCR) V gene usage has been used to characterize the immune response to bacteria, viruses, allografts, self antigens, tumor antigens, and superantigens. Sensitive methods to detect changes in the frequency of TCR subfamilies or clonotypes might be useful in evaluating the efficacy of vaccines against infectious agents, immunotherapy treatments for cancer patients, or the status of autoimmune diseases. Two HLA-A2 restricted CTL clones expressing BV17 were isolated from a tumor infiltrating lymphocytes (TIL) culture of a patient with metastatic melanoma. One clone recognized the MART-1 ((27-35)) peptide and the other clone recognized the gp100((209-217)) peptide. The frequency of each of these CTL clones in an expanding TIL culture was measured using a novel competitive RT-PCR (cRT-PCR) strategy. cRT-PCR uses a single primer pair to amplify template cDNA simultaneously with a modified DNA competitor molecule. A rapid two-step PCR technique followed by a single cloning step was used to generate a TCR BV17 subfamily specific competitor or competitors specific for the MART -1((27-35)) reactive CTL clone (CO-41) and the gp100((209-217)) reactive CTL clone (CO-4). Each competitor contained a segment of the TCR BC region that served as an internal reference standard. Using the BV17 competitor we were able to accurately and reproducibly measure cDNA templates at a frequency as low as 1/100,000 using cDNA samples of known TCRBV subfamily composition. This competitor was used to monitor the frequency of BV17 expressing T cells in the TTL and PMBC of a patient with metastatic melanoma. We determined that the frequency of BV17 expressing T cells increased from 4.5% of the culture on day 35 to 60.7% of the culture on day 58. Expansion of the BV17 subfamily was due predominantly to the expansion of the CO-4 clone. This method can be used to meaningfully quantify the precursor frequency of T cell mRNA in prepared samples via TCR subfamily or TCR sequence specific primers.

L10 ANSWER 14 OF 24 SCISEARCH COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:861069 SCISEARCH <<LOGINID::20090701>>
THE GENUINE ARTICLE: 137DB
TITLE: Ex vivo staining of metastatic lymph nodes by class I major histocompatibility complex tetramers reveals high numbers of antigen-experienced tumor-specific cytolytic T lymphocytes
AUTHOR: Romero P (Reprint)
CORPORATE SOURCE: CHU Vaudois, Ludwig Inst Canc Res, Div Clin Oncoimmunol, Lausanne Branch, BH 19-602, CH-1011 Lausanne, Switzerland (Reprint)
AUTHOR: Dunbar P R; Valmori D; Pittet M; Ogg G S; Rimoldi D; Chen J L; Lienard D; Cerottini J C; Cerundolo V
CORPORATE SOURCE: CHU Vaudois, Ludwig Inst Canc Res, Div Clin Oncoimmunol, Lausanne Branch, CH-1011 Lausanne, Switzerland; CHU Vaudois, Multidisciplinary Oncol Ctr, CH-1011 Lausanne, Switzerland; John Radcliffe Hosp, Inst Mol Med, Nuffield Dept Med, Oxford OX3 9DS, England
COUNTRY OF AUTHOR: Switzerland; England
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (2 NOV 1998) Vol. 188, No. 9, pp. 1641-1650.
ISSN: 0022-1007.
PUBLISHER: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021 USA.

DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 22
ENTRY DATE: Entered STN: 1998
Last Updated on STN: 1998
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Characterization of cytolytic T lymphocyte (CTL) responses to tumor antigens has been impeded by a lack of direct assays of CTL activity. We have synthesized reagents ("tetramers") that specifically stain CTLs recognizing melanoma antigens. Tetramer staining of tumor-infiltrated lymph nodes ex vivo revealed high frequencies of tumor-specific CTLs which were antigen-experienced by surface phenotype. In vitro culture of lymph node cells with cytokines resulted in very large expansions of tumor-specific CTLs that were dependent on the presence of tumor cells in the lymph nodes. Tetramer-guided sorting by now cytometer allowed isolation of melanoma-specific CTLs and confirmation of their specificity and their ability to lyse autologous tumor cells. Our results demonstrate the value of these novel reagents for monitoring tumor-specific CTL responses and for generating CTLs for adoptive immunotherapy. These data also indicate that strong CTL responses to melanoma often occur in vivo, and that the reactive CTLs have substantial proliferative and tumoricidal potential.

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ACCESSION NUMBER: 2000370788 EMBASE <<LOGINID::20090701>>
TITLE: Identification of human melanoma antigens recognized by tumor infiltrating T lymphocytes and their use for immunotherapy.
AUTHOR: Kawakami, Y. (correspondence)
CORPORATE SOURCE: Division of Cellular Signaling, Inst. for Advanced Medical Research, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
SOURCE: Gann Monographs on Cancer Research, (1999) Vol. 48, pp. 179-189.
Refs: 30
ISSN: 0072-0151 CODEN: GANMAX
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 013 Dermatology and Venereology
016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Nov 2000
Last Updated on STN: 16 Nov 2000

AB Adoptive transfer of cultured tumor infiltrating T-lymphocytes (TIL) with interleukin 2 (IL2) resulted in tumor regression in melanoma patients, indicating the important role of T-cells in mediating in vivo melanoma regression. TIL secrete cytokines and lyse tumor cells in vitro by recognizing autologous melanoma. Using cDNA expression cloning methods with these TIL, cDNAs encoding melanoma antigens including 5 melanosomal proteins (MART-1, gp100, tyrosinase, TRP1, and TRP2), p15 and β-catenin, were identified. Non-mutated and mutated T cell epitopes have also been identified. A variety of mechanisms to generate these T cell epitopes on melanoma has been identified including peptides derived from regular open reading frames (ORFs), an alternative ORF, introns, or sequences with a mutation. Some melanoma epitopes had relatively low major histocompatibility complex (MHC) binding affinities, suggesting that these

were subdominant self epitopes. Several MART-1 and gp100 epitopes were recognized by TIL from many patients, suggesting that these were immunodominant common epitopes. By in vitro stimulation with these identified epitopes, melanoma reactive cytotoxic T lymphocytes (CTL) could be efficiently induced from peripheral blood lymphocytes (PBL) or TIL of melanoma patients. Since adoptive transfer of the TIL reacting to these melanoma antigens into autologous patients with IL2 resulted in tumor regression, these peptides may function as tumor rejection antigens. Tumor regression correlated with vitiligo development after IL2 based immunotherapies in melanoma indicating that these epitopes may also be present on the surface of melanocytes in vivo and that autoreactive T-cells may be involved in the tumor regression. A variety of Phase I clinical trials including immunization with the MART-1 and gp100 peptides, or recombinant viruses containing the MART-1 or gp100 gene, with or without administration of cytokines such as IL2, granulocyte macrophagecolony stimulating factor (GM-CSF), IL12, is being conducted in the Surgery Branch of the National Cancer Institute (NCI), and tumor regression has been observed in some patients.

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ACCESSION NUMBER: 2000252605 EMBASE <<LOGINID::20090701>>

TITLE: Identification of tumor antigen-specific cytotoxic T lymphocytes cross-recognizing allogeneic major histocompatibility class I molecules.

AUTHOR: Fleischhauer, Katherina, Dr. (correspondence); Gattinoni, L.; Lietti, G.; Zino, E.; Bordignon, C.; Traversari, C.

CORPORATE SOURCE: Cancer Immunol. Immunotherapy Prog., Istituto Scientifico H.S. Raffaele, via Olgettina 58, I-20132 Milan, Italy. fleisck@tigem.it

SOURCE: Tissue Antigens, (2000) Vol. 56, No. 1, pp. 19-29. Refs: 40
ISSN: 0001-2815 CODEN: TSANA2

COUNTRY: Denmark

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 3 Aug 2000
Last Updated on STN: 3 Aug 2000

AB Adoptive immunotherapy of cancer utilizes tumor antigen-specific cytotoxic T lymphocytes (CTL) as mediators of a targeted anti-tumor effect. In this study, we show that such CTL can be able to cross-recognize allogeneic major histocompatibility complex (MHC) molecules in a phenomenon of molecular mimicry. A self histo-leukocyte antigen (HLA) A*0201- restricted CTL specific for peptide MT27-35 from the human differentiation antigen Melan-A/MART-1 was shown to cross-recognize allogeneic A*0220 molecules which differ from syngeneic A*0201 for a single amino acid substitution at position 66 of the antigen-binding groove. A*0220 molecules were recognized on a variety of human cells of different histological origin but not on COS-7 cells. A second self-A*0201-restricted CTL, specific for peptide D10/6-271 encoded by the tumor-specific DAM-gene family, was shown to cross-recognize allogeneic B*3701 molecules which differ from syngeneic A*0201 by 32 amino acids in the peptide antigen-binding cleft. B*3701 molecules were recognized on a variety of cell types including COS-7 cells. These data raise new safety issues for clinical trials of cancer immunotherapy using adoptive transfer of in vitro generated, allogeneic CTL with specific anti-tumor activity.

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ACCESSION NUMBER: 2000189304 EMBASE <<LOGINID::20090701>>
TITLE: New cancer therapy by immunomanipulation: Development of immunotherapy for human melanoma as a model system.
AUTHOR: Kawakami, Yutaka, Dr. (correspondence)
CORPORATE SOURCE: Division of Cellular Signaling, Inst. for Advanced Medical Research, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. yutakawa@med.keio.ac.jp
SOURCE: Cornea, (May 2000) Vol. 19, No. 3 SUPPL. 1, pp. S2-S6. Refs: 27
ISSN: 0277-3740 CODEN: CORNDB
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Jun 2000
Last Updated on STN: 15 Jun 2000

AB Purpose and Methods. T cells play an important role in in vivo rejection of human melanoma. Human melanoma antigens recognized by autologous T cells were identified. These antigens are classified as tissue (melanocyte)- specific proteins, cancer-testis antigens (proteins expressed in normal testis and various cancers), tumor-specific peptides derived from mutations in tumor cells, and others. Results. A variety of mechanisms generating T cell epitopes on tumor cells were discovered. Various clinical observations, including tumor regression observed in adoptive transfer of gp 100-reactive T cells suggest that these identified melanoma peptides may function as tumor rejection antigens. Immunodominant common epitopes that could expand melanoma-reactive cytotoxic T lymphocytes (CTLs) in vitro were found in the MART-1 and gp 100 antigens. New immunization protocols - including immunization with peptides, recombinant viruses, plasmid DNAs, and dendritic cells pulsed with peptides as well as adoptive transfer of in vitro-generated CTLs by stimulation with antigenic peptides - were developed (phase I clinical trials have been performed in the Surgery Branch of the National Cancer Institute, Bethesda, MD, U.S.A.). Immunization with the gp100(209(210M)) peptide that was modified to have high HLA-A2 binding affinity, along with incomplete Freund's adjuvant and interleukin (IL)-2, resulted in a 42% response rate in patients with melanoma. Conclusion. These immunotherapies need further improvement due to the mechanisms of tumor escape from T cell responses.

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ACCESSION NUMBER: 2000149900 EMBASE <<LOGINID::20090701>>
TITLE: High avidity melanoma-reactive cytotoxic T lymphocytes are efficiently induced from peripheral blood lymphocytes on stimulation by peptide-pulsed melanoma cells.
AUTHOR: Gervois, Nadine; Labarriere, Nathalie; Le Guiner, Soizic; Fonteneau, Jean-Francois; Guilloux, Yannik; Diez, Elisabeth; Jotereau, Francine (correspondence)
CORPORATE SOURCE: Institut de Biologie, INSERM U463, 44093 Nantes Cedex 1, France. jotereau@nantes.inserm.fr
AUTHOR: Pandolfino, Marie-Christine
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AUTHOR: Jotereau, Francine (correspondence)
CORPORATE SOURCE: Inst. Natl. S. de la Rech. Med. U463, 9 Quai Moncousu, 44093 Nantes Cedex 1, France. jotereau@nantes.inserm.fr
AUTHOR: Jotereau, Francine (correspondence)
CORPORATE SOURCE: Institut National de la Sante, Recherche Medicale U463, 9 Quai Moncousu, 44093 Nantes Cedex 1, France. jotereau@nantes.inserm.fr
SOURCE: Clinical Cancer Research, (Apr 2000) Vol. 6, No. 4, pp. 1459-1467.
Refs: 36
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
016 Cancer
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 May 2000
Last Updated on STN: 18 May 2000

AB To design an efficient procedure to expand high avidity melanoma reactive T cells and to perform immunotherapies, we compared conditions of peripheral blood lymphocyte (PBL) stimulation by Melan-A/MART-1 peptides. Avidity of induced CTLs was evaluated by measuring their lysis and cytokine secretion to peptide-pulsed transporter-associated protein-deficient cells and to melanoma cells. In side-by-side experiments, we show that melanoma cells, either allogeneic or autologous, induced the growth of high avidity Melan-A-reactive CTLs from all donors, whereas essentially low avidity T cells were induced by peptide-pulsed PBLs. We also show that at least two cytokines, interleukin-6 and interleukin-2, were required to promote the growth of high avidity CTLs. Once sorted by tetramer labeling or cloning, the specificity and reactivity to tumor cells of peptide-specific T cells induced by allogeneic melanoma cells were confirmed. We then describe a relatively simple and efficient procedure that allowed us to obtain systematically high amounts (in the range of billion) of high avidity Melan-A/MART-1-specific T cells from the PBLs of HLA-A2 melanoma patients and healthy donors in 3 months. Because this antigen is expressed by most melanoma tumors, this procedure should be useful for checking the efficiency of adoptive immunotherapy of melanoma tumors and using functionally well-defined Melan- A/MART -1-specific CTLs in a large group of patients.

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ACCESSION NUMBER: 1999223358 EMBASE <<LOGINID::20090701>>
TITLE: Efficient transfer of a tumor antigen-reactive TCR to human peripheral blood lymphocytes confers anti-tumor reactivity.
AUTHOR: Clay, Timothy M.; Custer, Mary C.; Sachs, Jessica; Hwu, Patrick; Rosenberg, Steven A.; Nishimura, Michael I., Dr. (correspondence)
CORPORATE SOURCE: Surgery Branch, National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, United States. nishimur@helix.nih.gov
SOURCE: Journal of Immunology, (1 Jul 1999) Vol. 163, No. 1, pp. 507-513.
Refs: 51
ISSN: 0022-1767 CODEN: JOIMA3

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Jul 1999
Last Updated on STN: 15 Jul 1999

AB The tumor-associated-Ag MART-1 is expressed by most human melanomas. The genes encoding an αβ TCR from a MART-1-specific, HLA-A2-restricted, human T cell clone have been efficiently transferred and expressed in human PBL. These retrovirally transduced PBL cultures were MART -1 peptide reactive, and most cultures recognized HLA-A2(+) melanoma lines. Limiting dilution clones were generated from three bulk transduced PBL cultures to investigate the function of individual clones within the transduced cultures. Twenty-nine of 29 CD8(+) clones specifically secreted IFN-γ in response to T2 cells pulsed with MART-1((27-35)) peptide, and 23 of 29 specifically secreted IFN-γ in response to HLA-A2(+) melanoma lines. Additionally, 23 of 29 CD8(+) clones lysed T2 cells pulsed with the MART-1(27-35) peptide and 15 of 29 lysed the HLA-A2(+) melanoma line 888. CD4(+) clones specifically secreted IFN-γ in response to T2 cells pulsed with the MART-1((27-35)) peptide. TCR gene transfer to patient PBL can produce CTL with anti-tumor reactivity in vitro and could potentially offer a treatment for patients with metastatic melanoma. This approach could also be applied to the treatment of other tumors and viral infections. Additionally, TCR gene transfer offers unique opportunities to study the fate of adoptively transferred T cells in vivo.

ACCESSION NUMBER: 1999159911 EMBASE <<LOGINID::20090701>>
TITLE: Potential use of T cell receptor genes to modify hematopoietic stem cells for the gene therapy of cancer.
AUTHOR: Clay, Timothy M. (correspondence); Custer, Mary C.; Spiess, Paul J.; Nishimura, Michael I.
CORPORATE SOURCE: Surgery Branch, National Cancer Institute, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892, United States. Tim_Clay@nih.gov.usa
SOURCE: Pathology Oncology Research, (Mar 1999) Vol. 5, No. 1, pp. 3-15.
Refs: 84
ISSN: 1219-4956 CODEN: POREFR
COUNTRY: Hungary
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 May 1999
Last Updated on STN: 27 May 1999

AB The purpose of this review is to illustrate some of the technical and biological hurdles that need to be addressed when developing new gene therapy based clinical trials. Gene transfer approaches can be used to 'mark' cells to monitor their persistence in vivo in patients, to protect

cells from toxic chemotherapeutic agents, correct a genetic defect within the target cell, or to confer a novel function on the target cell. Selection of the most suitable vector for gene transfer depends upon a number of factors such as the target cell itself and whether gene expression needs to be sustained or transient. The TCR gene transfer approach described here represents one innovative strategy being pursued as a potential therapy for metastatic melanoma. Tumor reactive T cells can be isolated from the tumor infiltrating lymphocytes (TIL) of melanoma patients. A retroviral vector has been constructed containing the T cell receptor (TCR) α and β chain genes from a MART- 1((27-35))-specific T cell clone (TIL 5). Jurkat cells transduced with this virus specifically release cytokine in response to MART-1 ((27-35)) peptide pulsed T2 cells, showing that the virus can mediate expression of a functional TCR. HLA-A2 transgenic mice are being used to examine whether transduced bone marrow progenitor cells will differentiate in vivo into mature CD8(+) T cells expressing the MART-1 ((27-35))-specific TCR. Expression of the human TCR α and β chain genes has been detected by RT-PCR in the peripheral blood of HLA-A2 transgenic mice reconstituted with transduced mouse bone marrow. Expression of the TIL 5 TCR genes in the peripheral blood of these mice was maintained for greater than 40 weeks after bone marrow reconstitution. TIL 5 TCR gene expression was also maintained following transfer of bone marrow from mice previously reconstituted with transduced bone marrow to secondary mouse recipients, suggesting that a pluripotent progenitor or lymphocyte progenitor cell has been tranduced.

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ACCESSION NUMBER:	1996207256 EMBASE <<LOGINID::20090701>>
TITLE:	Human melanoma antigens recognized by T lymphocytes.
AUTHOR:	Kawakami, Yutaka, Dr. (correspondence); Robbins, Paul F.; Rosenberg, Steven A.
CORPORATE SOURCE:	Surgery Branch, National Cancer Institute, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892-1502, United States.
SOURCE:	Keio Journal of Medicine, (Jun 1996) Vol. 45, No. 2, pp. 100-108. Refs: 78 ISSN: 0022-9717 CODEN: KJMEA9
COUNTRY:	Japan
DOCUMENT TYPE:	Journal; General Review; (Review)
FILE SEGMENT:	013 Dermatology and Venereology 016 Cancer 026 Immunology, Serology and Transplantation
LANGUAGE:	English
SUMMARY LANGUAGE:	English
ENTRY DATE:	Entered STN: 14 Aug 1996 Last Updated on STN: 14 Aug 1996

AB Human melanoma antigens and their epitopes recognized by T cells have been identified using a variety of methods. These antigens are classified as 1) melanocyte specific melanosomal proteins (MART-1, gp100, tyrosinase and TRP-1), 2) proteins expressed in testis and a variety of cancers (MAGE-1, MAGE-3, BAGE and GAGE), 3) tumor specific mutated proteins (β-catenin, MUM-1 and CDK4), and 4) others (p15). Some of the HLA-A2 binding non-mutated melanoma epitopes contained non-dominant anchor amino acids and have relatively low HLA-A2 binding affinity, suggesting that these epitopes were likely to be subdominant or cryptic self determinants. The significant correlation observed between vitiligo development and IL2 based immunotherapy suggested that autoreactive T cells specific for these self peptides were involved in

melanoma regression in vivo. In addition, since adoptive transfer into patients of CTL recognizing these epitopes resulted in tumor regression, these epitopes may be tumor rejection antigens. Melanoma reactive CTL were efficiently induced from PBL of patients by in vitro stimulation wilh PBMC pulsed with these melanoma epitopes and may be useful in adoptive transfer protocols for the treatment of patients with metastatic melanoma. An immunization trial using the MART-1 and gp100 peptides in conjunction with incomplete Freund's adjuvant is in progress. These identified antigens may be useful for the development of new immunotherapies for the treatment of melanoma patients as well as for understanding the mechanisms of anti-tumor immune responses and autoimmune disorders against melanocytes.

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ACCESSION NUMBER: 1995116989 EMBASE <<LOGINID::20090701>>
TITLE: Recognition of multiple epitopes in the human melanoma antigen gp100 by tumor-infiltrating T lymphocytes associated with in vivo tumor regression.
AUTHOR: Kawakami, Y., Dr. (correspondence); Eliyahu, S.; Jennings, C.; Sakaguchi, K.; Kang, X.; Southwood, S.; Robbins, P.F.; Sette, A.; Appella, E.; Rosenberg, S.A.
CORPORATE SOURCE: Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, United States.
SOURCE: Journal of Immunology, (1995) Vol. 154, No. 8, pp. 3961-3968.
ISSN: 0022-1767 CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 May 1995
Last Updated on STN: 3 May 1995

AB Four of ten HLA-A2-restricted melanoma specific CTL that were derived from tumor-infiltrating lymphocytes (TIL) and administered to patients recognized the gp100 melanoma Ag and nine of ten recognized the MART-1 Ag. Adoptive transfer of the four gp100-reactive CTL, but not the other TIL, resulted in tumor regression when infused into autologous patients along with IL-2. Tumor regression was thus correlated with the recognition of gp100 by the administered T cells (p = 0.0048). To identify the epitopes recognized by these four gp100-reactive CTL, 169 peptides containing HLA-A2.1 binding motifs were synthesized and screened for their recognition by TIL using cytotoxicity and IFN-γ release assays. Five gp100 epitopes (two for TIL620, three for TIL660, one for TIL1143, and two for TIL1200) were recognized by CTL derived from different patients. Five of eight HLA-A2 binding melanoma epitopes (five gp100, one MART-1/Melan-A, two tyrosinase) had intermediate binding affinity to HLA-A2.1. These gp100 epitopes may be responsible for mediating tumor rejection in vivo and thus may be useful for the development of immunotherapies for patients with melanoma.

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ACCESSION NUMBER: 1995065269 EMBASE <<LOGINID::20090701>>
TITLE: Induction of tumor-reactive CTL from peripheral blood and tumor- infiltrating lymphocytes of melanoma patients by in vitro stimulation with an immunodominant peptide of the human melanoma antigen MART-1.

AUTHOR: Rivoltini, L.; Kawakami, Y., Dr. (correspondence); Sakaguchi, K.; Southwood, S.; Sette, A.; Robbins, P.F.; Marincola, F.M.; Salgaller, M.L.; Yannelli, J.R.; Appella, E.; Rosenberg, S.A.

CORPORATE SOURCE: Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, United States.

SOURCE: Journal of Immunology, (1995) Vol. 154, No. 5, pp. 2257-2265.
ISSN: 0022-1767 CODEN: JOIMA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 14 Mar 1995
Last Updated on STN: 14 Mar 1995

AB MART-1 is an Ag expressed on melanomas and melanocytes, and is recognized by the majority of HLA-A2-restricted tumor-specific tumor-infiltrating lymphocytes (TIL) from melanoma patients. In the present study we have analyzed 10 potential 9-mer epitopes containing the HLA-A2.1 binding motifs for their ability to induce melanoma-specific T cell lines. Antimelanoma CTL could be generated only with MART-1(27-35) peptide, which has been previously shown to be recognized by a majority of HLA-A2-restricted TIL. Anti-MART-1(35-43)-specific CTL could also be induced, but these T cells did not recognize melanoma cells. MART-1(27-35)-specific CTL could be effectively generated from a total of 11 of 12 PBL and from 3 of 3 TIL derived from HLA-A2(+) melanoma patients, as well as from 2 of 4 PBL from HLA- A2(+) healthy donors by in vitro stimulation with autologous PBMC pulsed with the synthetic MART-1(27-35) peptide. These CTL lines specifically lysed and release cytokines (TNF-α, IFN-γ, and GM-CSF) in response to T2 cells pulsed with MART -1(27-35), as well as to HLA-A2(+) MART-1(+) melanoma cells. CTL generated with MART-1(27-35) also lysed uncultured HLA-A2(+) melanoma cells derived from tumor biopsies, indicating that this MART-1 epitope is likely to be expressed in association with HLA-A2 on the surface of tumor cells in vivo. CTL lines generated with MART-1(27-35) mediated 25- to 100- fold higher lytic activity than MART-1 -reactive CTL grown from TIL in the presence of high dose IL-2. These results demonstrate that MART-1(27-35) peptide may represent an ideal candidate for Ag-specific immunotherapy in melanoma patients.

L10 ANSWER 24 OF 24 EMBASE

ACCESSION NUMBER: 1995054471 EMBASE <<LOGINID::20090701>>

TITLE: Characterization of the functional specificity of a cloned T-cell receptor heterodimer recognizing the MART-1 melanoma antigen.

AUTHOR: Cole, David J. (correspondence); Weil, Daniel P.; Shilyansky, Joel; Custer, Mary; Kawakami, Yutaka; Rosenberg, Steven A.; Nishimura, Michael I.

CORPORATE SOURCE: Surgery Branch, National Cancer Institute, NIH, Bethesda, MD 20892, United States.

AUTHOR: Cole, David J. (correspondence)

CORPORATE SOURCE: Medical University of South Carolina, Department of Surgery, 171 Ashley Ave., Charleston, SC 29425-2270, United

States.
AUTHOR: Cole, David J. (correspondence)
CORPORATE SOURCE: Department of Surgery, Medical University of South Carolina, 171 Ashley Ave., Charleston, SC 29425-2270, United States.
SOURCE: Cancer Research, (15 Feb 1995) Vol. 55, No. 4, pp. 748-752. Refs: 26
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 8 Mar 1995
Last Updated on STN: 8 Mar 1995

AB T cells can play a central role in the immune response to cancer, with tumor-specific T-lymphocyte reactivity provided by the T-cell receptor (TCR) α and β chain heterodimer. This study is the first report of the definitive identification and characterization of a functional tumor-associated, antigen-specific TCR by reconstitution in an alternate cell line. Jurkat T cells were transfected with the cDNAs encoding the full-length α and β T- cell receptor chains from the HLA-A2 restricted, melanoma-reactive T-cell clone, clone 5. Expression of the transfected TCR was evaluated by immunofluorescence after down-modulation of the endogenous receptor with Jurkat T-cell receptor β chain-specific mAb. Jurkat clone 5 TCR(+) cells recognized MART-1 peptides presented by T2 cells in a pattern and sensitivity equivalent to native MART-1 -reactive T-cells. Recognition of HLA-A2+ melanoma cell lines by the Jurkat clone 5 TCR(+) cells, however, did not occur without the addition of exogenous MART-1 peptide. The cloning and expression of functional TCR genes which are capable of specifically recognizing MART-1 antigen provides reagents which could be used for the study of the mechanisms of T-cell /tumor antigen interactions and creates immortalized reagents which can facilitate studies requiring detection of the MART-1 antigen. The tumor reactivity provided by these genes could also have application in novel immunotherapeutic strategies for treating patients with melanoma, including redirection of tumor-infiltrating lymphocyte specificity and bone marrow stem cell therapy.

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